

(9)

REMARKS

By this amendment claims 25-26 are cancelled, claim 27 is amended and claims 36-43 are new. Claims 1-24 were previously cancelled and claims 28-34 were previously withdrawn.

Claim 27 has been amended by specifying that the method relates to the treatment of allergy and asthma patients in need of such treatment, based for example on the original claim 5. Claim 27 formerly referred to claim 25 and this has now been replaced by a positive recitation that the treatment comprises administering a pharmaceutical composition consisting essentially of glycophosphopeptical. Claim 27 has also been clarified by stating that the administration takes place in multiple doses for a short term treatment period of 1-20 days. Basis for multiple doses comes for example from page 8 lines 14-15. The 1-20 day treatment period is disclosed on original page 10, lines 7-10. The period of remission produced by the treatment has been specified as "several months", based for example on page 7, line 21 ("a long-term clinical remission of months..."). For clarity, it has been specified that further treatment is not necessary during the remission period, which is inherent from the direct meaning of remission since clearly the remission of the ailment means that the patient is not in need of further treatment.

New claim 35 specifies that the short term treatment period lasts 3-5 days, based for example on page 8, line 14.

New claim 36 specifies that the glycophosphopeptical is administered in doses up to 2000mg, for example based on page 8 line 16 and new claim 37 specifies 200-1000mg, based for example also on page 8, line 16.

New claim 38 specifies that the glycophosphopeptical is administered in doses at least once daily up to 10 times daily: see page 8, line 15.

New claim 39 specifies that the glycophosphopeptical is administered orally as capsules, tablets, lozenges, a powder or a syrup, as disclosed at page 8 lines 17-18.

New claim 40 specifies that the glycophosphopeptical is administered topically in the form of eye or nasal preparations such as drops or ointment, or skin or vaginal preparations such as cream and ointment, as disclosed on page 8, lines 18-20

New claim 41 specifies the treatment of patients suffering from extrinsic asthma, intrinsic asthma or mixed extrinsic/intrinsic asthma, based for example on page 8, line 26.

New claim 43, which specifies the treatment of patients suffering from allergic and perennial rhinitis, allergic conjunctivitis, chronic urticaria, atopic dermatitis or laryngeal oedema, is based for example on page 8, lines 26-28.

New claim 44 relates to treating patients suffering from chronic corticosteroid-dependent allergy and asthma. The treatment of chronic disease is stated on page 7, line 20 for example and this is taken in conjunction with the description on page 2, line 19 to page 2, line 10 of the known corticosteroid therapy.

### **Information Disclosure Statement**

Will be filed by mail

### **Claim Rejections 35 USC §102**

Claim 27, as previously worded, has been rejected under 35 U.S.C.102(b) as being anticipated by Sanchez Palacios A. et al Allergol Immunopathos (Madr)(1992), Vol. 20(1), pages 35-39 ("Sanchez").

The Applicants respectfully traverse this rejection for the following reasons:

- 1) Sanchez relates to the treatment of asthmatic bronchitis (which is not asthma) and infectious respiratory disorders.
- 2) Sanchez does not teach a short term treatment followed by a long term remission as required by amended claim 27.

The Applicants will develop these two lines of argument below.

1. Asthmatic bronchitis /asthma and infectious respiratory disorders

(11)

As stated in the Office Action, Sanchez discloses the use of immunoferon (AM3) in the treatment of childhood respiratory pathology. AM3 is the same as glycophosphopeptidal as claimed in claim 27.

The skilled person is aware that asthmatic bronchitis is a name given to -----

Thus, the skilled person understands that Sanchez relates to the treatment of infectious respiratory disorders, and did not treat the group of children for asthma or allergy which are non-infectious disorders

2. Short term treatment followed by a long term remission

Sanchez teaches the treatment of children with infectious disorders such as asthmatic bronchitis (not asthma) by administering 2 envelopes (1.g) daily for 4 months. Thus Sanchez does not disclose a treatment of asthma/allergy by multiple doses for a short term treatment period of 1-20 days, preferably 3-5 days, to induce a remission of several months during which further treatment is not necessary. In fact, since Sanchez's treatment extended over 4 months (about 120 days) it has to be considered a long term treatment of the infectious respiratory disorders.

It follows that amended claim 27 is novel over Sanchez.

Moreover, the Applicants submit that the subject matter of amended claim 27 is unobvious and inventive over the state-of-art and in particular over Sanchez, for the following reasons.

The claimed invention relates to the treatment of allergy and asthma in patients in need of such treatment.

Conventional treatments for these non-infectious disorders are treatments with corticosteroids and antileukotrienes as discussed in the application on page 1, line 21 to page 2, line 10.

(14)

**U. S. Patent and Trademark Office**  
**Request for Continuous Examination**  
**Fax No.: + 571-273-8300**

**My Reference: Patent Application Number: 09/944,564**

Date: May 22, 2008  
Total number of pages:

**Fax letter**

**Response to Office Action dated 07/11/2006 (Final Rejection)**  
**by submitting**  
**Request for continuous Examination**

Dear Sir:

In response to the above-identified final rejection of my patent application claims 25-27, may I kindly submit the following response:

- 1- By submitting a RCE form
- 2- Payment by Credit Card. Form PTO-2038 is attached.
- 3- Objection to the Examiner decision by submitting further evidence from medical textbooks clarifying the point of dispute with the examiner; in relation to the definition of asthma and asthmatic bronchitis, and differentiating them as unrelated separate medical entities, thus rendering my claims in the use of glycophosphopeptical in the treatment of asthma patentable and valid.
- 4- Amendment of claim 25, currently reads as “ “. May I kindly request separation of the use of glycophosphopeptical in the treatment of allergy from its use in the treatment of asthma. Discussion of the use in the treatment of allergy are part of the response to Office Action dated XXXX and filed on the XXXXX

**Response to Office Action dated 07/11/2006 (Final Rejection)**

In this Office Action the Examiner have raised the following points:

**Election/Restriction**

1. Applicant's election with traverse Group I in the reply filed on Aug 4, 2004 is acknowledged.
2. Claims 28-34 are withdrawn as being withdrawn to a non elected invention:

Reply: Agree

HS

## **Information Disclosure Statement**

3. The listing or citing of references in applicant's response is not a proper information disclosure statement.

### **Applicant's Response Dated April 12, 2006**

4. Claims 25-34 are pending. Claims 28-34 are withdrawn from further consideration as being drawn on nonelected invention. An action on the merit of claims 25-27 is considered herein below.

5. The rejection of claims 25-27 under 35 U. S. C. 102(b) as being anticipated by Sanchez Palacios A. et. Al. is maintained for the reasons of record as set forth in the Office Action dated November 21, 2005.

### **Rejection of Record Set Forth in the Office Action Dated November 21,2005**

6. The text of those actions .....

7. Claims 25-27 are rejected under 35 U. S. C. 102(b) as being anticipated by Sanchez Palacios A. et. al. Allergol Immunopathos (Madr) (1992), Vol 20 (1), pages 35-39 (Sanchez).

Sanchez discloses the use of Immunoferom (AM3) in the treatment of childhood infectious respiratory pathology. To assess the immunoclinical effectiveness of a biologic response immunomodulator, glycophosphopeptide (AM3) was administered to 20 children with asthmatic bronchitis. .... ect

8. Applicant's argument filed April 12, 2006 have been fully considered but they are not persuasive.....

Applicant's arguments have been considered but are not deemed germane. Sanchez teaches the use of glycophosphopeptide for treating asthmatic bronchitis. It was well known in the art at the time of the invention that asthmatic bronchitis is a condition in which the airways in the lung are obstructed due to both persistent asthma and bronchitis. Thus, the patient population treated by the method of Sanchez embraces asthma patients and therefore meets the limitation of the instantly claimed invention.

**Reply to points 4 – 7 inclusive and point 8 that are raised by the Examiner.**

### **The Examiner Search Strategy and Results 06-2802006**

The confusion arises because we are dealing with diseases clinically presented with cough wheeze and dyspnoea

I am still arguing that asthma and asthmatic bronchitis are separate unrelated diseases “confusion in the name” by the old terminology of “asthmatic bronchitis” [They also use a term of “cardiac asthma” to denote dyspnoea with heart failure (Annex II)]), and that the use of glycophosphopeptidase in asthma is novel. Therefore, I am submitting new clear medical evidence that clarifies the correlation between asthma and asthmatic bronchitis; according to Caroline Breese Hall and John T. McBride selected from Annex I: “We are dealing with two separate diseases that may coexist in an infant, and that children with bronchiolitis in infancy have no increased risk of asthma by the time they reach adolescence.” This will be detailed further in the following text. May I kindly ask the Examiner to consider this new evidence.

Selected chapters are photocopied, and the relevant paragraphs are underlined in order to clarify the source of confusion in the name, the differentiating clinical features, and the correlation between asthmatic bronchitis and asthma. I am trying to keep the text minimal, but excuse me for placing some paragraphs and sentences of secondary importance to keep the continuity of the reply. May I kindly ask the Examiner to consider this new evidence

New clear scientific and medical evidence are being submitted that clarifies the correlation between asthma and asthmatic bronchitis “We are dealing with two separate diseases that may coexist in an infant, and that children with bronchiolitis in infancy have no increased risk of asthma by the time they reach adolescence.” This will be detailed further, and are selected from Annex I- Caroline Breese Hall and John T. McBride. Bronchiolitis. Chapter 60: 812-819. PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES. Sixth Edition 2005. Elsevier Churchill Livingstone.

Selected from the textbook of Principles and Practice of Infectious Diseases 2005 (Annex 1), Dr. Caroline Breese Hall and John T. McBride in the chapter titled “Bronchiolitis”, are clarifying “the source of confusion in the name;” “We are dealing with two separate diseases that may coexist in an infant up to 2 years of age, and that children with bronchiolitis in infancy have no increased risk of asthma by the time they reach adolescence.” (page XXX coloum XX paragraph XX).

“Bronchiolitis is an acute viral lower respiratory tract illness that occurs during the first 2 years of life. The illness also has been called “wheezy bronchitis” and “asthmatic bronchitis”. Whatever term is applied, the syndrome is caused primarily by viral infections. The characteristic clinical manifestations include an acute onset of wheezing and hyperinflation, most commonly associated with cough, rhinorrhea, tachypnoea (increased respiratory rate) and respiratory distress.” (page XXX coloum XX paragraph XX).

“The term bronchiolitis appears to have been born from a long lineage of confusing sobriquets, including “acute catarrhal bronchitis,” “interstitial bronchopneumonia,” “spastic bronchopneumonia,” “capillary or obstructive bronchiolitis,” and “asthmatic

(15)

bronchitis." Bronchiolitis, however, did not become recognized as a distinct entity until the 1940s." (page XXX coloum XX paragraph XX).

### **Terminology or Definitions**

The term asthma, historically, is used to designate any disease characterized by "asthma-like symptoms", that are unrelated to the disease entity of current asthma. It has been used to describe patients complaining of shortness of breath (dyspnoea), wheeze (audible respiration), cough and sputum. As an example of this is the term cardiac asthma (a clinical manifestation of heart failure) and asthmatic bronchitis (a viral respiratory disease affecting infants and young children below 2 years of age)

#### **1- Cardiac Asthma**

Is a clinical manifestation of heart failure. Cardiac asthma is closely related to paroxysmal nocturnal dyspnoea and nocturnal cough and is characterized by wheezing secondary to bronchospasm-most prominent at night.

- Part VIII Disorders of the Cardiovascular System. HARRISON'S PRINCIPLES OF INTERNAL MEDICINE. 16<sup>th</sup> Edition (2005): page 1370. Mc Graw-Hill

#### **2- Asthmatic Bronchitis**

Caroline Breese Hall and John T. McBride. Bronchiolitis. Chapter 60: 812-819. PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES. Sixth Edition 2005. Elsevier Churchill Livingstone.

#### **Annexes:**

Annex 1. Caroline Breese Hall and John T. McBride. Bronchiolitis. Chapter 60: 812-819. PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES. Sixth Edition 2005. Elsevier Churchill Livingstone.

## **Claims**

### **Detailed Reply**

#### **Summary**

The search conducted by The Examiner according to PAIR is related to the disease groups manifested clinically by the triad of cough dyspnoea and wheeze and possible

diseases that can cause this triad are acute respiratory viral infection in the first 2 years of life in asthmatic bronchitis (bronchiolitis), or allergic relapsing as in asthma and as a result of smoking in chronic obstructive pulmonary disease (COPD).

The correlation between asthma and asthmatic bronchitis according to Annex I, and as detailed below

In page 812, column 2, the following statement is written:

**"Bronchiolitis is an acute viral lower respiratory tract illness that occurs during the first 2 years of life. The illness has been called "Wheezy bronchitis" and "asthmatic bronchitis."**

In page 816, column 1, under the subtitle Diagnosis, the following statement is written:

"The diagnosis of bronchiolitis is made most frequently on the basis of the characteristic clinical and epidemiologic findings. However, considerable confusion exists over the exact definition of bronchiolitis. A variety of entities may cause similar picture of dyspnoea and wheezing in the infant. Asthma is not easily differentiated, particularly if it is the infant's first episode. Furthermore, the two diseases may be combined.

In page 815, column 1, last paragraph, the following statement is written:

"Nevertheless, the association between bronchiolitis and asthma is not straightforward. Several investigators have demonstrated that children with bronchiolitis in infancy have no increased risk of asthma or abnormal pulmonary function by the time they reach early adolescence."

	Asthmatic bronchitis (Bronchiolitis)	Bronchial asthma
Age limitation		
Causative agent	Respiratory syncytial virus	Type I hypersensitivity reaction
Pathophysiology	Tissue necrosis,	Bronchoconstriction, mucosal edema, excessive secretion
Clinical presentation	Wheeze, dyspnoea, cough and sputum	Wheeze, dyspnoea, cough and sputum
Treatment	Antiviral agents	Bronchodilators, inhaled corticosteroids as controller medications, anti-leukotriens and others

Annex I- Caroline Breese Hall and John T. McBride. Bronchiolitis. Chapter 60: 812-819.  
PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES. Sixth Edition 2005.  
Elsevier Churchill Livingstone.

(17)

## Asthmatic Bronchitis (Bronchiolitis)

### Annex I

Detailed description of this disease was available from a textbook of "Principles and Practice of Infectious Diseases".

Bronchiolitis is an acute viral lower respiratory tract illness that occurs during the first 2 years of life. The illness also has been called "wheezy bronchitis" and "asthmatic bronchitis". Whatever term is applied, the syndrome is caused primarily by viral infections. The characteristic clinical manifestations include an acute onset of wheezing and hyperinflation, most commonly associated with cough, rhinorrhea, tachypnoea (increased respiratory rate) and respiratory distress.

The term bronchiolitis appears to have been born from a long lineage of confusing sobriquets, including "acute catarrhal bronchitis," "interstitial bronchopneumonia," "spastic bronchopneumonia," "capillary or obstructive bronchiolitis," and "asthmatic bronchitis." Bronchiolitis, however, did not become recognized as a distinct entity until the 1940s.

Etiology (P 812):

Respiratory syncytial virus (RSV) is clearly the major pathogen, and the parainfluenza virus is the second most commonly isolated agent.



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# Valoración clínica inmunológica de un modificador de la respuesta biológica, AM3, en el tratamiento de la patología respiratoria infecciosa infantil

A. Sánchez Palacios, J. A. García Marrero y F. Schamann A. T.

Servicio de Alergología. Hospital Insular. Las Palmas.

## SUMMARY

To assess the immunoclinical effectiveness of a biological response immunomodulator, we used AM3 (glycophosphopeptidic), a glucosmannan polysaccharide extracted from the cell wall of a strain of *Candida utilis*, in 20 children with asthmatic bronchitis. They received 2 envelopes (1 g) daily for 4 months.

The results were compared with a control group of 20 untreated children with the same pathology. The following clinical and immunological parameters were assessed in all of them: cough, dyspnea, expectoration, frequency and intensity of the bronchospasm, time of administration of the symptomatic medication, and the delayed cutaneous cells response by means of the intradermor reaction of 5 antigens (*Trichophyton*, *Candida albicans*, tuberculin, *E. coli* and bacterial antigens).

In the treated group, the immunoferon (AM3) reduced the symptoms, the intensity and frequency of the bronchospasm, and the symptomatic medication (table I, II and III).

In basal conditions, the 40 children presented a state of 75% anergy; after 4 months of treatment, the treated group experienced a 45% decrease in their anergic situation, variation which was statistically significant when compared with the control group.

In our 20 treated patients, AM3 behaved like an immunostimulant, improving the clinical situation and progress in patients with infectious respiratory disorders. We consider that the immunoferon constitutes a coadjuvant therapy to bacterial immunotherapy.

**Key words:** AM3. Biological response in children. Immunoferon in bronchial asthma.

Allergol. et Immunopathol., 20, 1 (35-39), 1992.

## INTRODUCCION

La presencia de un agente extraño en un organismo vivo superior va a dar lugar a una respuesta biológica frente a la agresión, cuyo fin inmediato es la eliminación del mismo.

Esta respuesta defensiva global suele comenzar con la puesta en marcha de mecanismos inespecíficos que forman parte de la respuesta inflamatoria y natural, ya que las dos se interrelacionan frecuentemente para concluir a menudo con una respuesta específica (inmune). Los aspectos cualitativos y cuantitativos de esta respuesta biológica dependen no solamente de la capacidad intrínseca del huésped para responder, sino también de aspectos del agente agresor.

Los modificadores de la respuesta biológica (MRB) han sido definidos como aquellos agentes capaces de modificar las relaciones entre un tumor y su huésped, mediante la manipulación de la respuesta biológica de éste hacia las células tumorales, consiguiendo resultados terapéuticos efectivos (1).

En patología oncológica e infecciosa los MRB pueden realizar sus acciones activando, amplificando o restaurando la reactividad de los mecanismos efectores defensivos o bien inhibiendo a los mecanismos supresores que intervienen negativamente, con la resistencia efectora defensiva del huésped.

El AM3 glicofosfopeptido es un polisacárido glucosmannano extraído de la pared celular de una cepa de *Candida utilis* por un proceso fermentativo y absorbido en una matriz inorgánica de fosfato y sulfato cálcicos.

Immunoferón es un modificador de la respuesta biológica con actividad restauradora inmunohematopoyética sobre los sistemas de inmunidad natural en huéspedes mielo y/o inmunocomprometidos.

En ensayos de farmacología experimental immunoferón ha demostrado recuperar la actividad citotóxica y antitumoral de células NK y macrófagos en animales inmunodeprimidos por ciclofosfamida y en animales de baja respuesta natural (15). Movilizan células efectoras de la respuesta natural inespecífica a focos inflamatorios no inmunogénicas (4). Incrementa la actividad fagocitaria y bactericida de macrófagos peritoneales y esplénicos frente a diversos agentes patógenos (5).

Bajo el punto de vista de la patología infecciosa, el interferón aumenta la resistencia frente a la infección

inteferon family

provocada por diferentes patógenos, incrementando la actividad bactericida y fagocitaria del macrófago (6, 7), mejora la respuesta terapéutica a los antibióticos en modelos experimentales de infección provocada (13).

El AM3 en tuberculosis pulmonar ha mejorado clínicamente bajo el punto de vista bacteriológico y radiológico en 40 pacientes hospitalizados (3). En broncopatías crónicas e infecciones ORL ha mejorado la evolución clínica reduciendo las recidivas (9, 12). En las profilaxis de infecciones respiratorias recidivantes, asociado a vacunoterapia, redujo significativamente la incidencia y duración de las crisis, la necesidad de instaurar antibióticos y el absentismo laboral por enfermedad (1).

El motivo del presente trabajo ha sido valorar la respuesta clínica inmunológica con AM3 en niños con patología infecciosa respiratoria.

## MATERIAL Y METODOS

Pacientes. Se seleccionaron 40 niños no atópicos con clínica respiratoria infecciosa de bronquitis espiráctica y/o asmática con pruebas cutáneas a neumolárgenos negativas e IgE total normal.

Se dividieron en 2 grupos para el estudio doble ciego de 20 cada uno. Grupo AM3, activo con tratamiento sintomático más inmunoferón sin inmunoterapia bacteriana. Grupo B, control sin inmunoferón con tratamiento sintomático.

Posología. Al grupo A se le administró 2 sobres diarios durante 4 meses (1 gramo diario de glicofosfopeptido).

Valoración clínica. Todos los pacientes acudían a nuestra unidad en régimen ambulatorio. En la primera visita, y a los 4 meses, se valoraban los siguientes parámetros clínicos: tratamiento sintomático (antibióticos, broncodilatadores, antitusivos y mucolíticos) y síntomas (tos, expectoración y disnea), valorándose de 1 a 4 según criterio: 1, ausente; 2, leve; 3, severo, y 4, muy severo. Broncospasmo: en frecuencia en 4 meses e intensidad según criterio: 1, ninguno; 2, reversible con medicación oral; 3, reversible con esteroides inyectables, y 4, reversible con ingreso en urgencias. Efectos secundarios.

Valoración inmunológica. Mediante pruebas intradérmicas para valorar la respuesta cutánea celular siguiendo el método clásico con una solución estéril de 0,1 ml de cada panel de 5 antígenos con control salino negativo. Los antígenos y diluciones recomendadas estándar han sido las de DTH (14). Incluyen los siguientes antígenos: Trichophyton (Dermatophytin «0» 1000 PNU/ml, Hollister-Stier, USA); Tuberculin (PPD RT23, 5TU/0,1 ml Cheminova, Espanic); *E. coli*, 1.106/ml, Abelló and antígeno bacteriano (vacuna bacteriana 750.106/ml Abelló).

La respuesta cutánea celular se valoraba a las 48 horas midiendo la induración (media de los valores de los diámetros perpendiculares).

Una reacción se consideraba positiva cuando la media de los diámetros fue de = 4 mm. A partir de éstos

Tabla I

Media de la intensidad de los síntomas tos, disnea y expectoración en condiciones basales y a los 4 meses

	Basal			4 meses		
	Tos	Disnea	Expect.	Tos	Disnea	Expect.
GM3 .....	3,1	3,8	2,9	1,9	2,1	1
GB.....	2,9	3,9	3,8	2,8	3	3,5

se establece el «score», suma de los diámetros medios de todas las reacciones positivas. Usando estos scores los 40 pacientes se clasificaron en 3 grupos: 1, anérgicos cuando los scores eran menor de 11 mm; 2, hipoérgicos cuando eran menor de 16 mm, y 3, normales cuando la respuesta era mayor o igual a 16 mm.

## RESULTADOS

La edad media de nuestros pacientes fue de 3 años y 7 meses, con un rango de 2-7 años. El tiempo de evolución de la enfermedad fue de 2 años y 4 meses y la distribución por sexos 11 niñas y 29 varones (36/72%). Por grupos AM3 (edad, 3,6; rango, 2-7; sexo, 6 h/14 v). GB (edad, 3,9; rango, 2-6; sexo, 5 h/15 v).

En la Tabla I vienen expresados la media de la intensidad de los síntomas tos, expectoración y disnea, en los grupos GM3 y GB en condiciones basales y a los 4 meses. Como puede observarse, la intensidad de los 3 síntomas es menor a los 4 meses en el grupo tratado con inmunoferón.

En la Tabla II vienen expresadas la frecuencia e intensidad del broncospasmo como la media del número de crisis de todos los pacientes en condiciones basales y a los 4 meses. El grupo AM3 presentó una disminución en intensidad y frecuencia de las crisis con respecto al B, con una  $p < 0,001$ .

En la Tabla III vienen reflejados el número de días con tratamiento antibióticos, mucolíticos y antitusígenos a lo largo de los 4 meses y la media del número de días por pacientes. En el grupo AM3 el consumo de antibióticos, mucolíticos y antitusígeno fue menor que el B, con una  $p < 0,001$ .

Tabla II

Media de la frecuencia e intensidad del broncospasmo

Grupos	Basal		4 meses	
	$\bar{x}$	$\bar{x}$	$\bar{x}$	$\bar{x}$
	N.º broncospasmo	Intens.	N.º broncospasmo	Intens.
AM3 .....	12	3,1	6,2	2,1
B .....	11,8	3,4	12	3

$p < 0,001$   
 $p NS$

Tabla III.

Tiempo de administración de la medicación sintomática

Tratamiento	AM3		Basal	
	Total días	Días/paciente x ± DS	Total días	Días/paciente x ± DS
Antibióticos ...	110	8 ± 2,1	220	21 ± 2,07
Mucolíticos ...	530	10 ± 2,5	890	40 ± 3,8
Antitusígenos .	80	740 ± 2,5	200	13 ± 3,2

En el grupo de los 20 pacientes tratados con inmunoferón AM3 no observamos efectos secundarios con la medicación a lo largo de los 4 meses. En las Tablas IV y V se expresan los resultados de la respuesta cutánea celular y se pueden observar cómo en condiciones basales ambos grupos AM3 y B tienen una respuesta celular similar, presentando anergia, es decir, una suma de scores menor de 11 mm en 16 pacientes y 14 para ambos grupos, lo que representa el 75% del total. En un estadio hipóergico aparecen el 25% restante, no existiendo una respuesta cutánea celular en ninguno de ellos.

Tras el tratamiento con inmunoferón en el grupo AM3, al cabo de 3 meses se modifica la respuesta cutánea celular, disminuyendo en 9 pacientes el estadio de anergia del 80 al 35%. Este hecho no ocurre con el grupo control B, en el cual la respuesta no se modifica con una p no significativa.

En la Figura 1 se expresan estos resultados en el eje de abscisas, se expresan el número de pacientes y en la ordenada los milímetros de la respuesta cutánea para ambos grupos; en condiciones basales los 2 grupos son homogéneos y a los 3 meses las 2 líneas en sus valores se cruzan, expresando la disminución de la anergia en el grupo tratado con inmunoferón, siendo la diferencia significativa con respecto a su situación basal p < 0,33.

Ninguno de los 20 pacientes tratados con 1 gramo de glicofosfopeptido durante los 4 meses tuvieron efectos secundarios y las cifras de calcemia no se modificaron.

## DISCUSION

La tórpida evolución que presentan muchos niños afectos de patología infecciosa respiratoria, sean o

Tabla IV

Respuesta cutánea celular (RCC) en condiciones basales

RCC	AM3 N.º de pacientes	GB N.º de pacientes
Anergia < 11 mm .....	16 (80%)	14 (70%)
Hipoérgicos < 16 mm ...	4 (20%)	6 (30%)
Normales ≥ 16 mm .....	0	0

Tabla V

Respuesta celular cutánea a los 4 meses de tratamiento

Resuestas	AM3	GB
Anergia < 11 mm .....	7 (35%)	16 (80%)
Hipoérgicas < 16 mm .....	13 (65%)	4 (20%)
Normales ≥ 16 mm .....	0	0

no atópicos, la achacamos a una falta de inmunoestimulación específica o inespecífica y del tratamiento sintomático, fundamentalmente la ausencia de antibioterapia.

La existencia de un foco infeccioso rinosinusal en el curso de un asma bronquial y/o bronquitis asmática empeora, desencadena o cronifica dicho proceso, de ahí la importancia de utilizar los antibióticos idóneos y la inmunoestimulación (10, 11, 14).

El AM3 (glicofosfopeptido) se comporta como un inmunomodulador de la respuesta biológica según trabajos publicados sobre farmacología experimental y clínica.

Muchos niños tienen alteraciones cualitativas y/o cuantitativas de la inmunidad humorar y celular en la respuesta biológica defensiva global. La disminución del sistema IgA secretor en el árbol respiratorio explicaría las reagudizaciones infecciosas respiratorias.

En nuestros 20 niños tratados se demuestra una mejoría clínica e inmunológica, tras los 3 meses con el AM3. La intensidad de los síntomas tos, expectoración y disnea disminuye, así como la frecuencia e intensidad del broncospasmo. La medicación sintomática, sobre todo antibióticos y antitusígenos, fue mejor que en el grupo control.

Para la valoración de la respuesta de hipersensibilidad cutánea retardada hemos utilizado la técnica clásica de intradermorreacciones a una batería de 5 antígenos; esta fue empleada siguiendo las recomendaciones vigentes para su aplicación e interpretación de forma estandarizada (2). Desechamos el Multitest CMI (Institute Merienx, Lyon, Francia), porque trabajos previos demuestran que la técnica clásica de intradermorreacciones tiene una sensibilidad superior al Multitest en la detección de anergia en la población

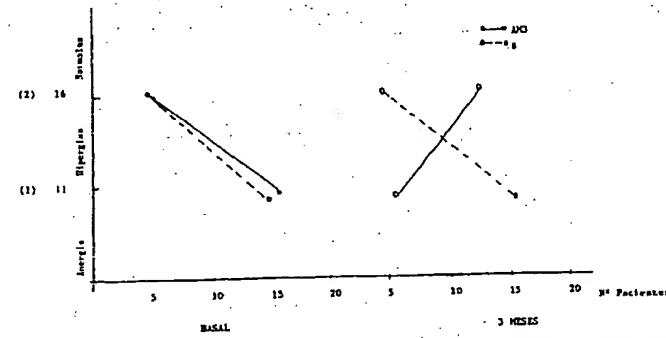


Fig. 1.—Evolución de la respuesta cutánea celular en 3 meses con y sin AM3.

inmunodeprimida y además reúne todos los criterios que requiere una batería de antigenos para medir la respuesta de hipersensibilidad cutánea retardada (6).

## RESUMEN

El AM3 (glicofosfopeptílico) es un polisacárido glucomanano extraído de la pared celular de una cepa de *Candida utilis*. Los ensayos de farmacología experimental y clínica han demostrado que el inmunoferón recupera la actividad citotóxica antitumoral, de células NK y macrófagos, moviliza células efectoras de la respuesta natural inespecífica a focos inflamatorios no inmunogénicos, incrementa la actividad bactericida, favorece la respuesta proliferativa T en algunas formas de inmunocompromiso inducido por citostáticos. Bajo el punto de vista clínico en tuberculosis pulmonar, broncopatías crónicas infecciosas ORL, herpes simple cutaneomucoso y en la profilaxis de infecciones respiratorias ha mejorado la evolución clínica en intensidad y recidivas, con reducción del tratamiento sintomático.

El propósito de nuestro trabajo ha sido valorar la eficacia clínica inmunológica de 20 pacientes afectos de bronquitis asmática. Recibieron 1 gramo diario de glicofosfopeptílico durante 4 meses. Los resultados se compararon con un grupo control de 20 niños no tratados con AM3 con la misma patología. En todos ellos se valoraron los siguientes parámetros clínicos e inmunológicos: tos, disnea, expectoración, frecuencia e intensidad del broncospasmo, tiempo de administración de la medicación sintomática y la respuesta cutáneo celular retardada mediante la intradermorreacción de 5 antigenos (*Trichophyton*, *Candida albicans*, *Tuberculin*, *E. coli* y antigenos bacterianos).

El inmunoferón (AM3) consigue en el grupo tratado una disminución de los síntomas, de la intensidad y frecuencia del broncospasmo y de la medicación sintomática. Modificó la respuesta cutánea celular en 9 pacientes que se encontraban en una situación de anergia, lo que representa un cambio inmunológico celular en un 45% de los pacientes tratados. Este hecho no ocurre con el grupo control, siendo la diferencia estadísticamente significativa. Pensamos que el AM3 constituye un tratamiento coadyuvante de la inmunoterapia bacteriana.

La tórrida evolución presentada por algunos niños con patología respiratoria infecciosa con o sin atopía la achacamos a la falta de una inmunoestimulación.

Con el propósito de valorar la eficacia clínica inmunológica de un inmunomodulador de la respuesta biológica utilizamos el AM3 (glicofosfopeptílico), que es un polisacárido glucomanano extraído de la pared celular de una cepa de *Candida utilis* en 20 niños afectos de bronquitis asmática. Recibimos 2 sobres diarios (1 g) durante 4 meses.

Los resultados se compararon con un grupo control de 20 niños con la misma patología no tratados. En todos ellos se valoraron los siguientes parámetros clínicos e inmunológicos: tos, disnea, expectoración, frecuencia e intensidad del broncospasmo, tiempo de

administración de la medicación sintomática y la respuesta cutáneo celular retardada mediante la intradermorreacción de 5 antigenos (*Trichophyton*, *Candida albicans*, *Tuberculin*, *E. coli* y antigenos bacterianos).

El inmunoferón (AM3) consigue en el grupo tratado una disminución de los síntomas, de la intensidad y frecuencia del broncospasmo y de la medicación sintomática (Tablas I, II y III).

En condiciones basales los 40 niños presentaron un estado de anergia en el 75%; a los 4 meses de tratamiento el grupo tratado experimentó una disminución de la situación de anergia en un 45%, siendo esta variación estadísticamente significativa con respecto al grupo control.

En nuestros 20 pacientes tratados el AM3 se comporta como un inmunoestimulante, mejorando la situación y evolución clínica en pacientes con patología respiratoria infecciosa. Pensamos que el inmunoferón constituye un tratamiento coadyuvante de la inmunoterapia bacteriana.

*it is an adjuvant for therapy with antibacterial therapy*

Palabras clave: AM3. Respuesta biológica en niños.

Inmunoferón en bronquitis asmática.

*in the treatment of asthmatic bronchitis*

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Annex III

# Mandell, Douglas, and Bennett's **Principles and Practice of Infectious Diseases**

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SIXTH EDITION

## **Gerald L. Mandell, MD, MACP**

Professor of Medicine  
Owen R. Cheatham Professor of the Sciences  
Division of Infectious Diseases  
University of Virginia School of Medicine  
Charlottesville, Virginia

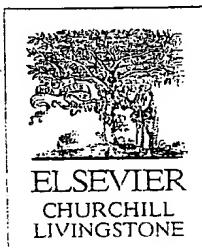
## **John E. Bennett, MD, MACP**

Adjunct Professor of Medicine  
Uniformed Services University of the Health Sciences  
Head, Clinical Mycology Section  
Laboratory of Clinical Infectious Diseases  
National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
Bethesda, Maryland

## **Raphael Dolin, MD**

Maxwell Finland Professor of Medicine (Microbiology and Molecular Genetics)  
Dean for Academic and Clinical Programs  
Harvard Medical School  
Boston, Massachusetts

**With illustrations by George V. Kelvin**



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## CHAPTER 60

### Bronchiolitis

CAROLINE BREESE HALL  
JOHN T. McBRIDE

*In bronchiolitis we must now contend  
with both the disease of the "now" and the "then";  
For many such infants a mold has been cast,  
perhaps by their unborn and unknown past,  
which destines that they shall in time wheeze again.  
For them this disease  
is the distant, boding knell  
of vulnerable lungs  
to a microbe's mystic spell.*

C.B.H.

**B**ronchiolitis is an acute viral lower respiratory tract illness that occurs during the first 2 years of life. The illness also has been called “wheezing bronchitis” and “asthmatic bronchitis.” Whatever term is applied, the syndrome is caused primarily by viral infections. The characteristic clinical manifestations include an acute onset of wheezing and hyperinflation, most commonly associated with cough, rhinorrhea, tachypnea, and respiratory distress.

The term *bronchiolitis* appears to have been born from a long lineage of confusing sobriquets, including “acute catarrhal bronchitis,” “interstitial bronchopneumonia,” “spastic bronchopneumonia,” “capillary or obstructive bronchiolitis,” and “asthmatic bronchiolitis.”<sup>11</sup> Bronchiolitis, however, did not become recognized as a distinct entity until the 1940s.<sup>1-5</sup>

### ETIOLOGY

Although bronchiolitis was initially thought to be caused by bacteria, viruses and occasionally *Mycoplasma pneumoniae* are now known to be the instigators. Respiratory syncytial virus (RSV) is clearly the major pathogen, and the parainfluenza viruses are the second most commonly isolated agents, with parainfluenza type 3 predominating (Table 60-1 and Fig. 60-1).<sup>6-8</sup> The recently discovered human metapneumovirus also produces bronchiolitis and appears to have clinical and epidemiologic characteristics similar to those of RSV.<sup>9,12</sup> The role of human metapneumovirus in causing respiratory illness in young children awaits further study, but information thus far suggests its contribution may be appreciable but secondary to that of RSV.

A long-term study of respiratory illnesses associated with wheezing in children from a private practice in Chapel Hill, North Carolina,

Agent	Cases (% of Total)	Epidemiologic Occurrence
Respiratory syncytial virus	40-80	Yearly epidemics, winter to spring
Parainfluenza viruses		
Type 3	8-15	Predominantly spring to fall
Type 1	5-12	Epidemics in fall every other year
Type 2	1-5	Fall
Rhinoviruses	3-8	Endemic, all seasons
Adenoviruses	3-10	Endemic, all seasons
Influenza viruses	6-8	Endemic, winter to spring
<i>Mycoplasma pneumoniae</i>	1-7	Endemic, all seasons
Enteroviruses	1-5	Summer to fall
Human metapneumovirus	Unknown	Predominately winter in some areas

showed that RSV, parainfluenza 1 and 3 viruses, adenoviruses, rhinoviruses, and *M. pneumoniae* make up 87% of the isolates obtained from children of all ages.<sup>6</sup> Within the first 2 years of life, RSV accounted for 44% of the isolates, with parainfluenza 1 and 3 viruses and adenoviruses each accounting for about 13%. Similarly, RSV constituted 60% of the isolates obtained from children with bronchiolitis from two group practices in Rochester, New York, over an 11-year period.<sup>13</sup> The second most frequently identified agent was parainfluenza 3 virus, which accounted for 12% of the cases. The relative proportions of these agents may change depending on the population and

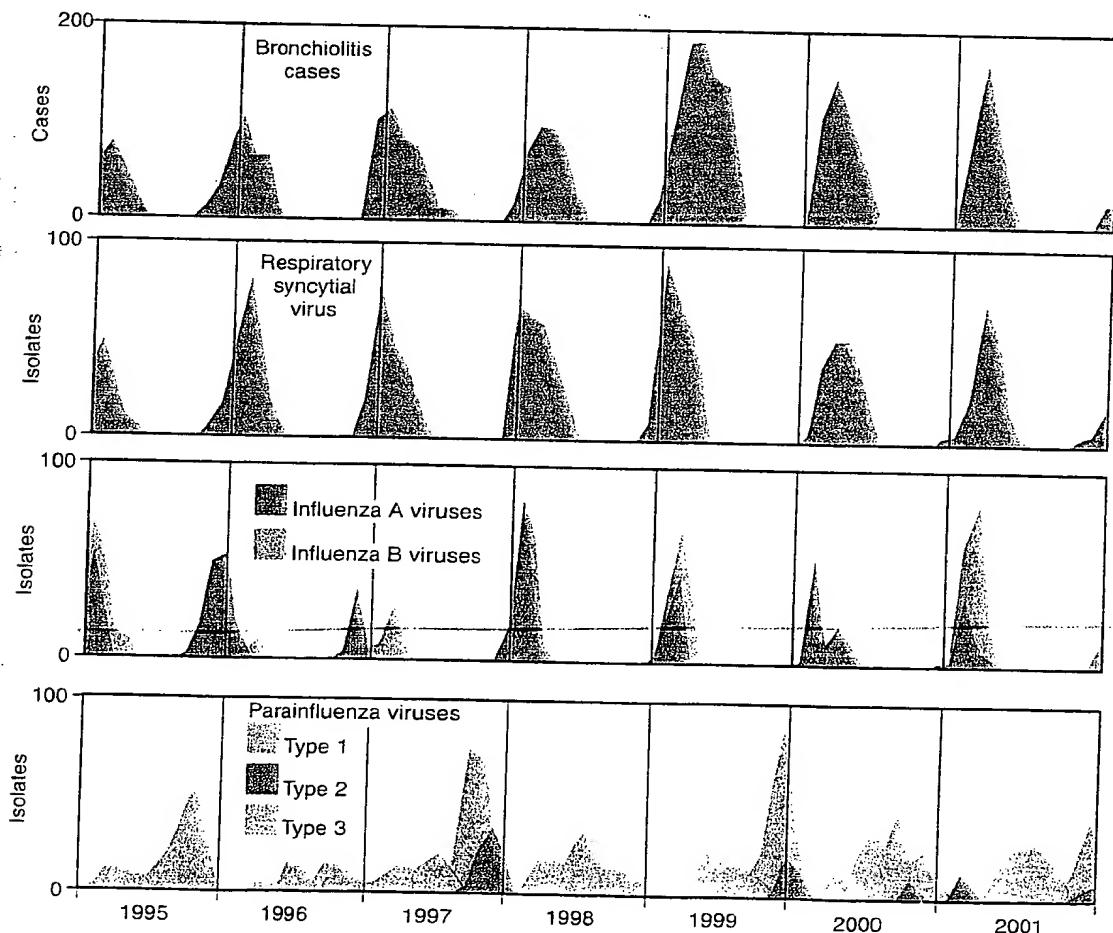
whether the cases occur as part of an outbreak. However, RSV remains the prime identified cause of bronchiolitis in most ambulatory patients and especially in hospitalized cases, and even in all lower respiratory tract admissions of young infants.<sup>1,4,14-17</sup>

## EPIDEMIOLOGY

Bronchiolitis shows a definite seasonal pattern in temperate climates, with a yearly upsurge in the number of cases during winter to early spring.<sup>6,8,13,18</sup> This pattern mirrors that of its prime agent, RSV (see Fig. 60-1). Lesser swells of activity are seen during the fall and spring, when parainfluenza viruses are active.

Bronchiolitis is a common illness during the first year of life, with the peak attack rate generally occurring between 1 and 10 months of age and between 5 weeks and 6 months in hospitalized cases.<sup>1,6,8,14,16,17,19</sup> In outpatients studied in Chapel Hill, the incidence of bronchiolitis was about 11 cases per 100 children for both the first and second 6 months of life.<sup>19</sup> In the second year of life, the incidence fell to approximately half that. Among children in the first year of life enrolled in a health maintenance organization in Tucson, Arizona, the rate of occurrence of lower respiratory tract illness was 32.9 cases per 100 children, and 60% of these cases were bronchiolitis.<sup>8</sup>

An appreciable proportion of hospital admissions for infants within the first year of life results from bronchiolitis, especially from RSV. In a review by Breese and colleagues, bronchiolitis was the reason for admission in 4% of their group-practice patients of all ages who required hospitalization for medical illnesses.<sup>19</sup> In a Seattle prepaid medical care group, the rate of hospitalization among infants with bronchiolitis



**FIGURE 60-1.** Patterns of reported cases of bronchiolitis shown in relation to the activity of the major respiratory viruses in Monroe County, New York. Data are obtained from a weekly community surveillance program for infectious disease.

during the first 6 months of life was 6 per 1000 children per year.<sup>5</sup> More recent studies using hospital discharge diagnoses have estimated that RSV caused 50% to 80% of hospitalizations of infants under 1 year of age with bronchiolitis, resulting in 73,400 to 126,300 admissions each year.<sup>16</sup> In this same age group, the RSV hospitalization rate has been estimated to be 25 to 41 per 1000 children.<sup>14,20</sup> RSV hospitalizations for all children under 5 years of age have been judged to be 110,000 each year, resulting in hospital costs of up to \$750 million.<sup>21,22</sup> Studies from the Centers for Disease Control and Prevention have estimated the associated mortality for bronchiolitis between 1979 and 1997 was 95 cases (range, 66 to 127) annually for children under 5 years of age, and in infants in the first year of life it was 2.0 per 100,000 live births from 1996 through 1998<sup>23-25</sup>; 55% of these deaths occurred in infants 1 to 3 months of age.

Bronchiolitis is more common in boys, especially among children requiring hospitalization, with a sex ratio of about 1.5 to 1.<sup>6</sup> Other factors described as increasing the chances of hospitalization for bronchiolitis in otherwise normal children include young age, being less than 6 months of age prior to onset of RSV season, young maternal age, lower cord blood antibody titers to RSV, lower socioeconomic status, tobacco smoke exposure, living in crowded surroundings, having older siblings, daycare attendance, lack of breast-feeding, a predisposition to atopy or hyperreactivity of the airway, and illness caused by RSV.<sup>3,6,26-28</sup> Infants at risk for most severe disease, however, are those with underlying conditions, especially cardiopulmonary disease, and preterm gestation.<sup>24</sup> In addition, certain ethnic groups of infants have higher rates of hospitalization for bronchiolitis. Native American and Native Alaskan children have been estimated to have two to three times higher rates than those for all infants in the United States.<sup>25,29</sup>

## PATOPHYSIOLOGY

The term *bronchiolitis* was first used by Engle and Newns in 1940 for the lower respiratory tract disease they observed in young infants that tended to be severe, often fatal, and that was probably viral in origin.<sup>12</sup> They carefully described the pathologic findings in these infants dying of bronchiolitis, which over the subsequent half century have been confirmed and expanded.<sup>30</sup>

The pathologic findings in bronchiolitis are characteristically focused on the respiratory epithelium with generalized involvement. The virus initially replicates in the epithelium of the upper respiratory tract, but in the young infant it tends to spread rapidly to the lower tract airways. Early inflammation of the bronchial and bronchiolar

epithelium progresses rapidly to necrosis. Subsequently, the epithelium may proliferate and demonstrate cuboidal cells without cilia. Peribronchiolar infiltration, mostly with mononuclear cells, and edema of the submucosa and adventitia occur, and these progress to the observed necrosis and sloughing of the bronchiolar epithelium (Figs. 60-2 and 60-3).

Inflammatory changes of variable severity are observed in most small bronchi and bronchioles. Because resistance to the flow of air is related inversely to the cube of the radius of the airway, the inflammation and edema make the small-lumen airways in infants particularly vulnerable to obstruction. Plugs of necrotic material and fibrin may completely or partially obstruct the small airways.

Smooth muscle constriction does not appear to be important in the obstruction. In areas peripheral to sites of partial obstruction, air becomes trapped by a process similar to a ball-valve mechanism. The negative intrapleural pressure exerted during inspiration allows air to flow beyond the point of partial obstruction. However, on expiration, the size of the lumen decreases with the positive pressure, thereby resulting in increased obstruction and hyperinflation. Thus, although airflow is impeded during both inspiration and expiration, the latter is more affected and prolonged. In areas peripheral to complete obstruction, the trapped air eventually becomes absorbed, which results in multiple areas of atelectasis. This absorptive atelectasis is greatly accelerated when the child is breathing high concentrations of oxygen. The degree of atelectasis or hyperinflation that develops may be greater in infants because collateral channels that maintain alveolar expansion in the presence of airway obstruction are not well developed early in life.

The physiologic correlates of this resistance to airflow are dyspnea, tachypnea, a diminished tidal volume, and a markedly altered distribution of ventilation. In significant areas of lung parenchyma, the ratio of ventilation to perfusion is low, and this produces arterial hypoxemia. When an infant is no longer able to compensate for the disordered gas exchange by increasing ventilation, hypercarbia may ensue. The pathologic process may progress to involve the alveolar walls and spaces, producing an interstitial pneumonitis. Recovery tends to be slow and requires several weeks.

Experimental and clinical studies have suggested that the development of wheezing and the pathogenesis of bronchiolitis in some children, and their risk for subsequent wheezing and pulmonary function abnormalities, are related to the type of inflammatory response initiated by RSV or other viruses and to a predisposition of the host (see Chapter 155). In particular, hypersensitivity responses characterized

**FIGURE 60-2.** Inflammation and necrosis in bronchiolitis, resulting in obliteration of the bronchiolar lumen.



by increased levels of virus-specific IgE antibody and certain cellular inflammatory mediators have been related to the development and severity of wheezing in infants and the risk of recurrent wheezing.<sup>31-33</sup> Studies detecting cytokines and chemokines in respiratory secretions of children with bronchiolitis and with recurrent wheezing have suggested the expression of interferon- $\gamma$ , interleukin (IL)-8, IL-10, and cytokines produced by helper T (Th)1 and Th2 lymphocytes are important in the pathogenesis of bronchiolitis and subsequent recurrent episodes of wheezing.<sup>31-38</sup>

Clarifying the relationship between bronchiolitis and subsequent asthma is complicated by confusion about the pathophysiology of asthma itself.<sup>39</sup> Asthma is a heterogeneous group of disorders engendered by multiple factors, both genetic and environmental. These include not only an atopic predisposition and the environmental risk factors noted earlier but also specific genetic polymorphisms.<sup>3,40-42</sup> Studies on twins have demonstrated that 70% of the risk of developing asthma in early childhood is related to genetic factors,<sup>43</sup> and many of the specific linkages identified to date are related to inflammation. Nevertheless, the disorders in this heterogeneous group share, in various combinations, wheezing, reversible airway obstruction, airway inflammation, and structural airway wall remodeling. Many distinct asthma phenotypes exist, and the following are examples of only three: (1) Some children wheeze repeatedly with respiratory viral infections in the first 5 years of life but have few problems thereafter.<sup>46</sup> (2) Other children with atopy and allergies develop wheezing beyond 5 years of age. Many of these have fewer problems when they become teenagers and adults. (3) Other individuals with adult-onset wheezing are at increased risk of developing irreversible airway obstruction.

Much of asthma, therefore, seems to be related to a dysregulation of airway inflammation. Inherited traits that do not involve the inflammatory response may also be important in some individuals, such as variations in the beta adrenergic receptor or in airway geometry (e.g., size). Any traits that contribute to the dysregulation of airway inflammation or airway dysfunction in asthma may also contribute to the same processes with respiratory viral infections. Thus, the increased incidence of wheezing with subsequent respiratory viral infections among children with a history of bronchiolitis in infancy is not surprising. Nevertheless, the association between bronchiolitis and asthma is not straightforward. Several investigators have demonstrated that children with bronchiolitis in infancy have no increased risk for asthma or abnormal pulmonary function by the time they reach early adolescence.<sup>47</sup>

## CLINICAL MANIFESTATIONS

Bronchiolitis may have a variety of appellations, including wheezing, bronchiolitis, infectious asthma, and asthmatic bronchitis, but all refer to the clinical syndrome in young children presenting with wheezing and hyperinflation of the lungs often accompanied by tachypnea. The onset of bronchiolitis, however, consists of upper respiratory tract signs, especially coryza and cough. Commonly, a prodromal period of 1 to 7 days occurs and is marked by fever, which is usually mild, especially with RSV. Sometimes the initial presentation is apnea. Apnea usually appears after 1 to 3 days of upper respiratory signs that are so mild as to go unnoticed and before lower respiratory tract disease is evident. Manifestations of lower respiratory tract involvement become evident after the several days of the prodromal upper respiratory tract signs. The progression of the disease may be reflected initially in the development of a prominent cough, and subsequently by an increase in the respiratory rate and in nonspecific systemic symptoms such as irritability, lethargy, and anorexia. With progression, tachypnea and tachycardia may be marked, although fever may no longer be present. Retractions of the chest wall, flaring of the nasal alae, and grunting are evidence of the increased work of breathing. Cyanosis is rarely observed, even though moderate to severe hypoxemia may be present.<sup>48</sup> Auscultatory findings, which may vary from hour to hour, include wheezing with or without crackles. Increasing dyspnea with decreasing lung sounds on auscultation and diminished movement of air may indicate progressive obstruction and impending respiratory failure.

Dehydration is a common accompaniment of bronchiolitis and results from paroxysms of coughing, which may trigger vomiting, and from a poor oral intake related to the respiratory distress and lethargy. Tachypnea further increases the fluid requirement. Otitis media occurs in 10% to 30% of infants, and mild conjunctivitis and occasionally diarrhea may also be present.

The acute course typically lasts 3 to 7 days. Most infants show improvement within 3 to 4 days and gradually recover over 1 to 2 weeks, but the cough may persist for longer. One study, examining the duration of illness in ambulatory children diagnosed with bronchiolitis, found that the median duration of symptoms was 12 days. After 3 weeks, 18% remained symptomatic, and after 4 weeks, 9% continued to be ill.<sup>49</sup> No factor—sex, age, weight, or respiratory rate—appeared to be predictive of longer illness. The viral etiology was not examined.

**FIGURE 60-3.** Inflammation of the bronchiole with regenerating epithelium.



## COMPLICATIONS

Almost all children recover from bronchiolitis without difficulty.<sup>3,49</sup> Complications from bronchiolitis are relatively rare, especially in normal children. A number of studies have attempted to predict by epidemiologic and clinical characteristics which children with acute bronchiolitis are most likely to have complicated or severe courses. Infants with underlying diseases, especially cardiac, pulmonary, and immunodeficiency diseases, and those who were premature are most at risk for prolonged or complicated illness.<sup>24,27,50,51</sup> Clinical characteristics at the onset of the acute illness, such as respiratory rate or auscultatory findings, have not been of consistent prognostic value. Diminished arterial oxygen saturation, however, has been associated with complicated illness.<sup>3,50,52</sup> Progression to respiratory failure and prolonged hypoxemia are uncommon with currently available technical and pharmacologic methods of management. If such complications occur, they are most likely to be in infants with compromising underlying conditions and in very young infants.

Cardiovascular abnormalities have been occasionally reported to occur during bronchiolitis in children with no underlying cardiac disease.<sup>53,54</sup> In one study, 2% of infants with bronchiolitis had mild electrocardiographic abnormalities.<sup>54</sup> In a small group of infants with bronchiolitis from RSV or parainfluenza virus, about half were demonstrated to have some transient tricuspid valve regurgitation during the most acute phase of the illness.<sup>53</sup>

Aspiration has also been demonstrated to be a relatively frequent complication in infants with RSV bronchiolitis.<sup>55,56</sup> Infants who received no therapy for aspiration were much more likely to develop reactive airway disease subsequently.

The sequelae of bronchiolitis that occur frequently and are of major concern are recurrent episodes of reactive airway disease, which are accompanied by pulmonary function abnormalities in some children. As discussed previously (see "Pathophysiology"), the link between this and bronchiolitis in infancy is unclear. Nevertheless, the prognosis for most children with subsequent episodes of wheezing during early childhood is good. Some follow-up studies of children who had bronchiolitis diagnosed in infancy have shown that these children at school age had no greater occurrence of reactive airway disease than those without an early history of bronchiolitis.<sup>57,58</sup> The mortality associated with bronchiolitis has been markedly reduced with the advancement in the technology of supportive care. Overall, the mortality in hospitalized infants has been estimated to be less than 1%.<sup>59,60</sup> The mortality rate, however, increases significantly in those children with underlying compromising conditions and is estimated at 3% to 5%.<sup>23,59</sup> In these children, the greatest proportion of bronchiolitis-associated deaths has occurred in infants of low birth weight (<2500 g), especially in those with very low birth weight (<1500 g).<sup>24</sup> Nevertheless, the majority (63%) of all bronchiolitis-associated deaths in children under 1 year of age occurs in those with a normal birth weight.<sup>24</sup>

## LABORATORY FINDINGS

The total white blood cell count in children with bronchiolitis is usually within the normal range or slightly elevated.<sup>3,48</sup> In hospitalized infants who are more seriously ill and hypoxic, the white blood cell count may be elevated, and the differential count may show a leftward shift. Most infants requiring hospitalization will have some degree of hypoxemia on measurement of the arterial oxygen saturation levels. Clinically, this is difficult to assess, because the degree of wheezing and retractions correlates poorly with the level of oxygenation. Only the most severely ill children develop hypercarbia, as most are able to compensate for the compromised gas exchange by increasing the minute ventilation despite the increased work of breathing.<sup>1</sup>

## DIAGNOSIS

The diagnosis of bronchiolitis is made most frequently on the basis of the characteristic clinical and epidemiologic findings. However, considerable confusion exists over the exact definition of bronchiolitis.<sup>61</sup>

A variety of entities may cause a similar picture of dyspnea and wheezing in the infant. Asthma is not easily differentiated, particularly if it is the infant's first episode. Furthermore, the two diseases may be combined. An appreciable proportion of wheezing episodes occurring in a child with an atopic diathesis may arise from viral infections.<sup>62</sup> RSV in particular has a propensity to induce wheezing in young children. Even in adults with acute RSV infection that is clinically manifested as an upper respiratory tract infection, hyperreactivity of the airways can be detected by pulmonary function testing and may last for 1 or 2 months.<sup>63</sup>

Specific laboratory and radiologic tests are not required for most cases of bronchiolitis.<sup>64</sup> In hospitalized infants, determination of the viral etiology may be helpful for infection control procedures, including cohorting, and when specific antiviral therapy, as for influenza or RSV, is being considered.<sup>51</sup>

Identification of the specific agent of acute bronchiolitis can be made in an appreciable proportion of infants by viral isolation from respiratory secretions, preferably from a nasal wash.<sup>65,66</sup> In most cases, the viruses associated with bronchiolitis may be identified in tissue culture within 3 to 7 days. More commonly used are the rapid viral diagnostic techniques, especially for RSV and influenza A and B viruses, which allow identification of the viral antigen in the respiratory secretions within hours.<sup>66,67</sup> The sensitivity of these assays is variable, and the positive predictive value significantly diminishes when RSV infection or the influenza viruses are not epidemic in the community. The use of culture in addition to the screening rapid antigen detection assay may be of particular benefit when the suspected viral agent is not highly prevalent in the community, and when results of the screening rapid-technique tests are negative. Viral isolation procedures and rapid antigen tests that include multiple viral antigens offer the further advantage of detecting other agents that may be the cause of the illness or that are concurrently present. The sensitivity of detecting the viral etiology appears to be markedly enhanced by the use of reverse transcriptase-polymerase chain reaction (RT-PCR).<sup>67-69</sup> Serologic tests to determine the etiologic agent are rarely helpful in clinical management and may be difficult to interpret, because the young infant has maternally acquired antibody to many of the viral agents of bronchiolitis.

A chest radiograph is not routinely recommended for first-time wheezers in the first year of life if there are no complications or underlying disease.<sup>3</sup> If a chest roentgenogram is obtained, the hallmarks of acute bronchiolitis are hyperinflation with associated depressed diaphragms, hyperlucency of the parenchyma, and decreased costophrenic angles.<sup>70-73</sup> The bronchovascular markings are usually prominent, with linear densities radiating from the hila. Multiple areas of atelectasis of variable degree are also commonly present and difficult to differentiate from the infiltrates of pneumonia. Indeed, both bronchiolitis and pneumonia may be concurrently present, especially with RSV infection.

The abnormalities observed on the chest roentgenogram in acute bronchiolitis often do not correlate with the degree of clinical illness; the child may be severely ill despite minimal findings on the chest roentgenogram. Furthermore, considerable intraobserver and interobserver variation has been observed to occur among radiologists in their assessment of roentgenographic findings for the diagnosis of lower respiratory tract disease in infants, especially those with bronchiolitis.<sup>73</sup>

The differential diagnosis of wheezing in an infant is broad and requires a careful history and examination.<sup>61</sup> Gastric reflux and aspiration may produce a picture that is indistinguishable clinically from acute bronchiolitis. Other considerations include obstruction of the airway by a foreign body, vascular rings, retropharyngeal abscess, and even enlarged adenoids. Wheezing may also be associated with cystic fibrosis, immunodeficiency, and congestive heart failure in young infants.

## THERAPY

Supportive care is the mainstay of therapy in both outpatient and inpatient cases. At home, care is aimed primarily at comfort, maintaining adequate hydration, and treating fever if necessary. Antibiotics are

not routinely recommended and should be reserved for cases in which proven coinfection with bacteria exists.<sup>3,64</sup>

Hospitalization is necessary for those infants unable to maintain adequate hydration and for those infants with evidence of increasing lethargy and respiratory distress. This may be signaled by increasing retractions of the chest wall and by tachypnea. However, determination of the respiratory rate in young infants is often confounded by crying and fever, and the normal respiratory rate according to age must be considered.<sup>3</sup>

More than two decades ago, Reynolds and Cook noted for hospitalized infants that "oxygen is vitally important in bronchiolitis, and there is little convincing evidence that any other therapy is consistently or even occasionally useful."<sup>74</sup> Today, the mainstay of therapy for the hospitalized child remains supportive care with oxygen administration to maintain an adequate oxygen saturation level (usually at 92% or greater).<sup>1,3,64,75</sup> Although mist therapy is also commonly employed, its use has not been proven beneficial, and chest physiotherapy has been shown to be of no help.<sup>76,77</sup>

The only specific therapy currently available for hospitalized cases of bronchiolitis caused by RSV is inhaled ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), a synthetic nucleoside (see Chapter 155). Ribavirin should be considered for therapy only for those infants who have or are at risk of developing severe or complicated RSV infection, such as those with underlying predisposing conditions, especially prematurity and cardiopulmonary disease.<sup>51</sup> The drug is expensive and the relative benefit to cost must be considered on the basis of the individual patient.

Medical therapy commonly includes bronchodilators, corticosteroids, and antibiotics. Evidence for use of any of these has been confusing, contrasting, or incomplete.<sup>64,78</sup> A recent review by the Agency for Healthcare Research and Quality<sup>64</sup> of the efficacy of these therapies in managing bronchiolitis concluded that no single agent could be routinely recommended for the management of bronchiolitis. Convincing evidence for the use of these or other agents was not identified, and some had adverse effects, including budesonide and interferon-alfa-2. The agency's review suggested that several agents should be further studied in correctly designed trials, including nebulized epinephrine, nebulized salbutamol plus ipratropium bromide, nebulized ipratropium bromide, oral or parenteral corticosteroids (preferably dexamethasone), and inhaled corticosteroids. Despite this lack of evidence of efficacy, these agents, including antibiotics, are used in the majority of infants hospitalized with bronchiolitis and with bronchiolitis identified as caused by RSV.<sup>79,80</sup>

One meta-analysis of bronchodilating agents concluded that no recommendation could be made because determination of their benefit was confounded by the various methods and populations included in the available studies.<sup>81</sup> However, a recent multicenter, randomized, double-blind, controlled study of infants less than 12 months of age with acute bronchiolitis demonstrated that therapy with nebulized epinephrine did not significantly shorten the duration of hospitalization, or the number of days until the infant was ready for discharge.<sup>78</sup> Furthermore, in the cohort of infants who required supplemental oxygen and intravenous fluids, the time until an infant was ready to be discharged was significantly longer for those who received nebulized epinephrine than for those who received placebo. These agents, therefore, are not routinely recommended for infants.<sup>3,64,82</sup> A carefully monitored trial of nebulized bronchodilators in individual cases has been recommended by some. The response should be objectively documented by diminished respiratory distress and improved oxygen saturation. An initial beneficial response, however, may not be seen when bronchodilators are again used later. Repeated use of inhaled bronchodilators in the absence of a positive clinical response is inappropriate.

Studies examining the benefit of corticosteroid therapy have included infants with a clinical diagnosis of bronchiolitis but without a determination of specific viral etiology. The results have been conflicting; most corticosteroids have shown no benefit, and their use is not routinely recommended.<sup>3,64,75</sup> A meta-analysis of therapy with systemic corticosteroids employed in six trials concluded that the duration of hospitalization and symptoms was shortened by 0.43 days.<sup>83</sup>

However, two of the six trials included infants with a history of previous wheezing. If these two studies were eliminated from the analysis, the remaining four studies with only first-time wheezers showed that corticosteroids had no significant benefit. Patients with underlying asthma or chronic lung disease (bronchopulmonary dysplasia) who have bronchiolitis related to a lower respiratory viral infection are much more likely to benefit from bronchodilator therapy or a brief course of corticosteroids than are previously well infants. Therefore, such therapy should be considered for infants with bronchiolitis who have bronchopulmonary dysplasia or chronic lung disease, a history of previous wheezing, or a strong family history of asthma.

## PREVENTION

Prevention of the clinical entity of bronchiolitis is very difficult because of its multiple etiologies and varying pathogenesis. For bronchiolitis associated with primary RSV infection, antibody preparations, including intravenous immunoglobulin and intravenous immunoglobulin with high titers of neutralizing antibody to RSV (RSV-IVIgG), and more recently monoclonal antibody directed against the F protein of RSV (palivizumab), have been examined for use therapeutically and prophylactically.<sup>51</sup> None of these preparations has shown any benefit in therapy. In high-risk infants, controlled trials have shown a significant reduction in hospitalization for RSV infection when RSV-IVIgG or palivizumab is given on a monthly basis over the 5-month period of RSV activity in the community.<sup>51</sup> Whether infants with high-risk conditions would derive significant benefit compared to the cost remains controversial and in general should be determined on the basis of each infant's circumstances and estimated risk.

## BRONCHIOLITIS OBLITERANS

A rare, chronic type of bronchiolitis termed bronchiolitis obliterans has been reported in both adults and children.<sup>84,85</sup> Bronchiolitis obliterans has been cited as an uncommon complication of viral infections, usually viral bronchiolitis, lung transplantation, connective tissue diseases, and inhalation of toxic substances. Often, no cause is identified.<sup>85,86</sup>

In infants, especially those with certain undefined genetic predispositions, the major association has been with adenovirus infection.<sup>87</sup> The disease appears to be particularly prevalent among Native American populations in central Canada and among Polynesians in New Zealand. In some geographic areas, the frequency or clustering of bronchiolitis obliterans cases has been correlated with the occurrence of adenoviral infection in the community.

## Pathogenesis

Bronchiolitis obliterans is believed to result from an injury to the bronchioles and smaller airways. The healing process produces large amounts of inflammatory cells, mucoid tissue, granulation tissue, and thickening of the airway walls with connective tissue. This subsequently produces obstruction, bronchiectasis, and even obliteration of the airways.<sup>88,89</sup>

## Clinical Findings

The respiratory illness in children initially appears similar to other viral lower respiratory tract illnesses, characterized by cough and lower respiratory tract signs. An interim period of improvement may occur, followed by progressive symptoms of respiratory distress, productive cough, and wheezing. The obstructive respiratory symptoms progress and persist, and the child becomes chronically ill. Many develop bronchiectasis, cor pulmonale, and dependence on oxygen.

## Diagnosis

A nodular, diffuse picture, similar to that for miliary tuberculosis, is present on chest roentgenogram. Some patients may also develop Swyer-James syndrome, characterized by a decrease in pulmonary vascular markings and unilateral hyperlucency. Computed tomography reveals bronchiectasis, and bronchography shows that the contrast does not reach the peripheral areas of the lung because of the obstruction.

Annex II

Allergies  
Cardiac asthma

16th Edition

# HARRISON'S PRINCIPLES OF Internal Medicine

*Editors*

## DENNIS L. KASPER, MD

William Ellery Channing Professor of Medicine,  
Professor of Microbiology and Molecular Genetics,  
Harvard Medical School; Director, Channing  
Laboratory, Department of Medicine, Brigham and  
Women's Hospital, Boston

## EUGENE BRAUNWALD, MD

Distinguished Hersey Professor of Medicine,  
Harvard Medical School; Chairman, TIMI Study Group.  
Brigham and Women's Hospital, Boston

## ANTHONY S. FAUCI, MD

Chief, Laboratory of Immunoregulation; Director,  
National Institute of Allergy and Infectious Diseases,  
National Institutes of Health, Bethesda

## DAN L. LONGO, MD

Scientific Director, National Institute on Aging,  
National Institutes of Health,  
Bethesda and Baltimore

## STEPHEN L. HAUSER, MD

Robert A. Fishman Distinguished Professor and Chairman,  
Department of Neurology,  
University of California San Francisco, San Francisco

## J. LARRY JAMESON, MD, PhD

Irving S. Cutter Professor and Chairman,  
Department of Medicine,  
Northwestern University Feinberg School of Medicine;  
Physician-in-Chief, Northwestern  
Memorial Hospital, Chicago

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water occurs as a consequence of the elevation of systemic venous and capillary pressures and the resultant transudation of fluid into the pulmonary or systemic interstitial space. On the other hand, proponents of the *forward HF* hypothesis maintain that the clinical manifestations of HF result directly from an inadequate discharge of blood into the arterial system. According to this concept, salt and water retention is a consequence of diminished renal perfusion and excessive proximal and distal tubular reabsorption of sodium, the latter through activation of the renin-angiotensin-aldosterone system (RAAS) (Chap. 32).

The rate of onset of HF often influences the clinical manifestations. For example, when a large portion of the left ventricle is suddenly destroyed, as in myocardial infarction, the patient may succumb to acute pulmonary edema, a manifestation of *backward failure*. If the patient survives the acute insult, clinical manifestations resulting from a chronically depressed cardiac output, including the abnormal retention of fluid within the systemic vascular bed, may develop, which is a manifestation of *forward failure*.

**SALT AND WATER RETENTION** (See also Chap. 32) When the volume of blood pumped by the left ventricle into the systemic vascular bed is reduced, a complex sequence of adjustments occurs that ultimately results in the abnormal accumulation of fluid. This may be considered a two-edged sword. Many of the troubling clinical manifestations of HF, such as pulmonary congestion and edema, are secondary to this excessive retention of fluid (see Fig. 32-1). However, this abnormal fluid accumulation and the expansion of blood volume that accompanies it also constitute an important compensatory mechanism that tends to maintain cardiac output and therefore perfusion of the vital organs. Except in the terminal stages of HF, the ventricle operates on an ascending, albeit depressed and flattened, function curve (see Fig. 215-5), and the augmented ventricular end-diastolic volume characteristic of HF must be regarded as helping to maintain the reduced cardiac output, despite causing pulmonary and/or systemic venous congestion.

#### CLINICAL MANIFESTATIONS OF HEART FAILURE

**RESPIRATORY DISTURBANCES** ■ **Dyspnea** (Chap. 29) In early HF, dyspnea is observed only during exertion, when it may simply represent an aggravation of the breathlessness that occurs normally. As HF advances, dyspnea occurs with progressively less strenuous activity and ultimately it is present even at rest. The principal difference between exertional dyspnea in normal persons and in patients with HF is the degree of exertion necessary to induce this symptom. Cardiac dyspnea is observed most frequently in patients with elevations of pulmonary venous and capillary pressures who have engorged pulmonary vessels and interstitial accumulation of interstitial fluid. The activation of receptors in the lungs results in the rapid, shallow breathing characteristic of cardiac dyspnea. The oxygen cost of breathing is increased by the excessive work of the respiratory muscles required to move air into and out of the congested lungs. This is coupled with the diminished delivery of oxygen to these muscles, a consequence of a reduced cardiac output. This imbalance may contribute to fatigue of the respiratory muscles and the sensation of shortness of breath.

**Orthopnea** This symptom, i.e., dyspnea in the recumbent position, is usually a later manifestation of HF than exertional dyspnea. Orthopnea results from the redistribution of fluid from the abdomen and lower extremities into the chest during recumbency, which increases the pulmonary capillary pressure, combined with elevation of the diaphragm. Patients with orthopnea must elevate their head on several pillows at night and frequently awaken short of breath and/or coughing if their head slips off the pillows. Orthopnea is usually relieved by sitting upright, and some patients report that they find relief from sitting in front of an open window. In advanced HF, patients cannot lie down at all and must spend the entire night in a sitting position.

**Paroxysmal (Nocturnal) Dyspnea** This term refers to attacks of severe shortness of breath and coughing that generally occur at night, usually

awaken the patient from sleep, and may be quite frightening. Though simple orthopnea may be relieved by sitting upright at the side of the bed with legs dependent, in the patient with paroxysmal nocturnal dyspnea, coughing and wheezing often persist even in this position. Paroxysmal nocturnal dyspnea may be caused in part by the depression of the respiratory center during sleep, which may reduce ventilation sufficiently to lower arterial oxygen tension, particularly in patients with interstitial lung edema and reduced pulmonary compliance. **Cardiac asthma** is closely related to paroxysmal nocturnal dyspnea and nocturnal cough and is characterized by wheezing secondary to bronchospasm—most prominent at night. **Acute pulmonary edema** (Chaps. 29 and 255) is a severe form of cardiac asthma due to marked elevation of pulmonary capillary pressure leading to alveolar edema, associated with extreme shortness of breath, rales over the lung fields, and the expectoration of blood-tinged fluid. If not treated promptly, acute pulmonary edema may be fatal.

**Cheyne-Stokes Respiration** Also known as *periodic respiration* or *cyclic respiration*, Cheyne-Stokes respiration is characterized by diminished sensitivity of the respiratory center to arterial  $P_{CO_2}$ . There is an apneic phase, during which the arterial  $P_O_2$  falls and the arterial  $P_{CO_2}$  rises. These changes in the arterial blood stimulate the depressed respiratory center, resulting in hyperventilation and hypocapnia, followed in turn by recurrence of apnea. Cheyne-Stokes respiration occurs most often in patients with cerebral atherosclerosis and other cerebral lesions, but the prolongation of the circulation time from the lung to the brain that occurs in HF, particularly in patients with hypertension and coronary artery disease, also appears to contribute to this form of disordered breathing.

**OTHER SYMPTOMS** ■ **Fatigue and Weakness** These nonspecific but common symptoms of HF are related to the reduction of skeletal muscle perfusion. Exercise capacity is reduced by the limited ability of the failing heart to increase its output and deliver oxygen to the exercising muscles.

**Abdominal Symptoms** Anorexia and nausea associated with abdominal pain and fullness are frequent complaints and may be related to the congested liver and portal venous system.

**Cerebral Symptoms** Patients with severe HF, particularly elderly patients with cerebral arteriosclerosis, reduced cerebral perfusion, and arterial hypoxemia, may develop alterations in the mental state characterized by confusion, difficulty in concentration, impairment of memory, headache, insomnia, and anxiety. **Nocturia** is common in HF and may contribute to insomnia.

**PHYSICAL FINDINGS** (See Chap. 209) In mild or moderately severe HF, the patient appears in no distress at rest except feeling uncomfortable when lying flat for more than a few minutes. In severe HF, the pulse pressure may be diminished, reflecting a reduction in stroke volume, and the diastolic arterial pressure may be elevated as a consequence of generalized vasoconstriction. In severe acute HF, systolic hypotension may be present, with cool, diaphoretic extremities, and Cheyne-Stokes respiration. There may be cyanosis of the lips and nail beds (Chap. 31) and sinus tachycardia. **Systemic venous pressure** is often abnormally elevated, and this may be reflected in distention of the jugular veins. In the early stages of HF, the venous pressure may be normal at rest but may become abnormally elevated, with sustained pressure on the abdomen (positive abdominojugular reflux).

Third and fourth heart sounds are often audible but are not specific for HF, and **pulsus alternans**, i.e., a regular rhythm with alternation of strong and weak cardiac contractions and therefore alternation in the strength of the peripheral pulses, may be present. This sign of severe HF may be detected by sphygmomanometry and in more severe cases even by palpation; it frequently follows an extrasystole and is observed most commonly in patients with cardiomyopathy, hypertensive, or ischemic heart disease.

**Pulmonary Rales:** Moist inspiratory, crepitant rales and dullness to percussion over the lung bases are common in patients with HF and el-

otomy (the Chamberlain procedure). This approach involves either a right or left parasternal incision and dissection directly down to a mass or node that requires biopsy.

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# Harrison's principles of Internal Medicine 2005

**236**

## ASTHMA

E. R. McFadden, Jr.

Asthma is defined as a chronic inflammatory disease of airways that is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli. It is manifested physiologically by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy, and clinically by paroxysms of dyspnea, cough, and wheezing. Asthma is an episodic disease, with acute exacerbations interspersed with symptom-free periods. Typically, most attacks are short-lived, lasting minutes to hours, and clinically the patient seems to recover completely after an attack. However, there can be a phase in which the patient experiences some degree of airway obstruction daily. This phase can be mild, with or without superimposed severe episodes, or much more serious, with severe obstruction persisting for days or weeks; the latter condition is known as *status asthmaticus*. In unusual circumstances, acute episodes can cause death.

**PREVALENCE AND ETIOLOGY** Asthma is a very common disease with immense social impact. The prevalence of asthma is rising in many parts of the world, but it is unclear whether this is due to an actual increase in incidence or merely to the fact that the size of the overall population is growing. It is estimated that 4 to 5% of the population of the United States is affected. Data from the Centers for Disease Control and Prevention suggest that 10 to 11 million persons had acute attacks in 1998, which resulted in 13.9 million outpatient visits, 2 million requests for urgent care, and 423,000 hospitalizations, with a total cost >\$6 billion. The impact of the disease appears to fall more heavily on minorities and inner-city African-American and Hispanic persons.

Bronchial asthma occurs at all ages but predominantly in early life. About one-half of cases develop before age 10, and another third occur before age 40. In childhood, there is a 2:1 male/female preponderance, but the sex ratio equalizes by age 30. From an etiologic standpoint, asthma is a heterogeneous disease and genetic (atopic) and environmental factors, such as viruses, occupational exposures, and allergens, contribute to its initiation and continuance.

Atopy is the single largest risk factor for the development of asthma. *Allergic asthma* is often associated with a personal and/or family history of allergic diseases such as rhinitis, urticaria, and eczema; with positive wheal-and-flare skin reactions to intradermal injection of extracts of airborne antigens; with increased levels of IgE in the serum; and/or with a positive response to provocation tests involving the inhalation of specific antigen.

A significant fraction of patients with asthma present with no personal or family history of allergy, with negative skin tests, and with normal serum levels of IgE, and therefore have disease that cannot be classified on the basis of currently defined immunologic mechanisms. These patients are said to have *idiosyncratic asthma* or *nonatopic asthma*. Many patients have disease that does not fit clearly into either of the preceding categories but instead falls into a mixed group with

## Section 2 Diseases of the Respiratory System

features of each. In general, asthma that has its onset in early life tends to have a strong allergic component, whereas asthma that develops late tends to be nonallergic or to have a mixed etiology.

**PATHOGENESIS** (See also Chap. 298) Asthma results from a state of persistent subacute inflammation of the airways. Even in asymptomatic patients, the airways can be edematous and infiltrated with eosinophils, neutrophils, and lymphocytes, with or without an increase in the collagen content of the epithelial basement membrane. Overall, there is a generalized increase in cellularity associated with an elevated capillary density. There may also be glandular hypertrophy and denudation of the epithelium. These changes may persist despite treatment and often do not relate to the severity of the disease.

The physiologic and clinical features of asthma derive from an interaction among the resident and infiltrating inflammatory cells in the airway surface epithelium, inflammatory mediators, and cytokines. The cells thought to play important parts in the inflammatory response are mast cells, eosinophils, lymphocytes, and airway epithelial cells. The roles of neutrophils, macrophages, and other cellular constituents of the airways are less well defined. Each of the major cell types can contribute mediators and cytokines to initiate and amplify both acute inflammation and the long-term pathologic changes described (Fig. 236-1). The mediators released produce an intense, immediate inflammatory reaction involving bronchoconstriction, vascular congestion, edema formation, increased mucus production, and impaired mucociliary transport. This intense local event can then be followed by a more chronic one. Other elaborated chemotactic factors (eosinophil and neutrophil chemotactic factors of anaphylaxis and leukotriene B<sub>4</sub>) also bring eosinophils, platelets, and polymorphonuclear leukocytes to the site of the reaction. The airway epithelium is both the target of, and a contributor to, the inflammatory cascade. This tissue both amplifies bronchoconstriction and promotes vasodilatation through the release of the compounds shown in Fig. 236-2.

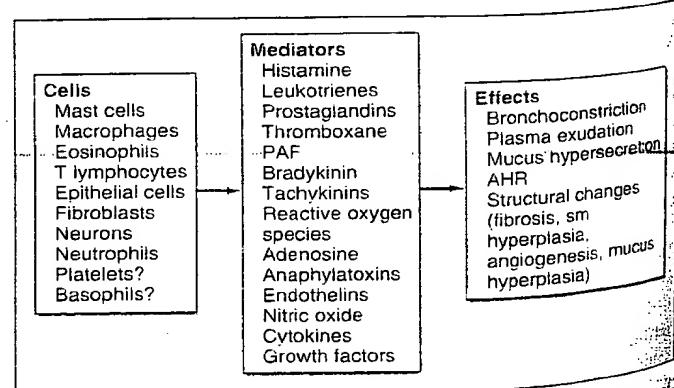
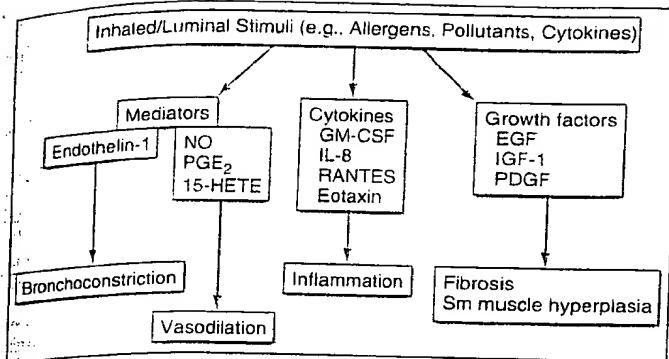


FIGURE 236-1 Cellular sources of inflammatory mediators and their physiologic effects. PAF, platelet-activating factor; AHR, antihistaminic reaction. [From PJ Barnes, in E Middleton et al (eds): *Allergy Principles and Practice*, 5th ed. St. Louis, Mosby, 1998, with permission.]



**FIGURE 236-2** Inflammatory mediators derived from epithelial sources. NO, nitrous oxide; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; RANTES, regulated on activation, T cell expressed and secreted; EGF, epidermal growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor. [From P. Barnes, in E Middleton et al (eds): *Allergy Principles and Practice*, 5th ed. St. Louis, Mosby, 1998, with permission.]

The eosinophil appears to play an important part in the infiltrative component. Interleukin (IL)-5 stimulates the release of these cells into the circulation and extends their survival. Once activated, these cells are a rich source of leukotrienes, and the granular proteins released (major basic protein and eosinophilic cationic protein) and oxygen-derived free radicals are capable of destroying the airway epithelium, which then is sloughed into the bronchial lumen in the form of Creola bodies. Besides resulting in a loss of barrier and secretory function, such damage elicits the production of chemotactic cytokines, leading to further inflammation. In theory, it can also expose sensory nerve endings, thus initiating neurogenic inflammatory pathways. That, in turn, could convert a primary local event into a generalized reaction via a reflex mechanism. Although an important element in inflammation, the role that the eosinophil plays in establishing and maintaining airway hyperresponsiveness is undergoing reevaluation. Studies using antibodies against IL-5 show a disassociation between the inflammatory and physiologic events following an antigen challenge and blood and sputum eosinophilia. The cytokine network possibly involved in asthma is shown in Fig. 236-3.

T lymphocytes also appear to be important in the inflammatory response. Activated T<sub>H</sub>2 cells are present in increased numbers in asthmatic airways and produce cytokines such as IL-4 that initiate humoral (IgE) immune responses. They also elaborate IL-5 with its effect on eosinophils. Data are accumulating that asthma may be related to an imbalance between T<sub>H</sub>1 and T<sub>H</sub>2 immune responses, but firm conclusions are not yet available.

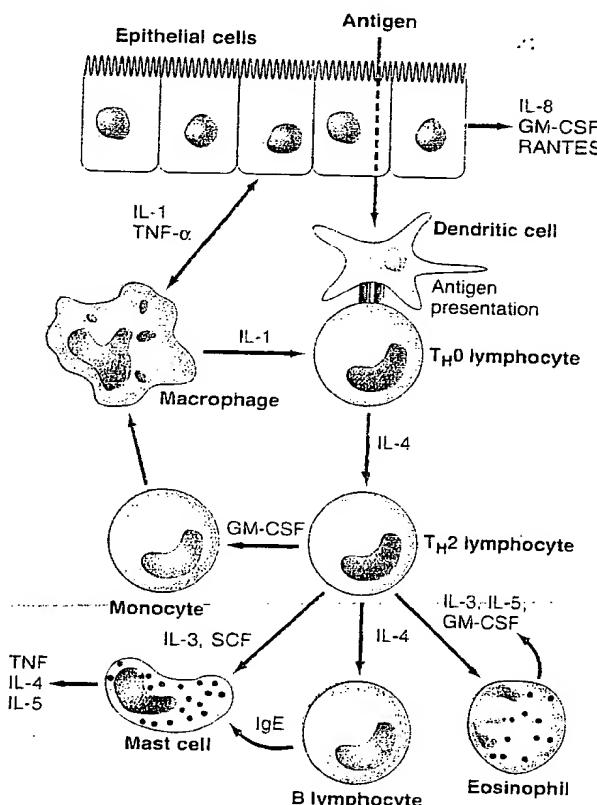
**GENETIC CONSIDERATIONS** Although there is little doubt that asthma has a strong familial component, the identification of the genetic mechanisms underlying the illness has proven difficult for such fundamental reasons as a lack of uniform agreement on the definition of the disease, the inability to define a single phenotype, non-Mendelian modes of inheritance, and an incomplete understanding of how environmental factors modify genetic expression. Screening families for candidate genes has identified multiple chromosomal regions that relate to atopy, elevated IgE levels, and airway hyperresponsiveness. Evidence for genetic linkage of high total serum IgE levels and atopy has been observed on chromosomes 5q, 11q, and 12q in a number of populations scattered throughout the world. Regions of the genome demonstrating evidence for linkage to bronchial hyperreactivity also typically show evidence for linkage to elevated total serum IgE levels. Excellent candidate genes exist for specific abnormalities in asthma within the regions that were identified in the linkage studies. For example, chromosome 5q contains cytokine clusters including IL-4, IL-9, and IL-13. Other regions on chromosome 5q also contain the adrenergic receptors and the glucocorticoid receptors. Chromosome 12q contains regions that are important in antigen presentation and me-

diation of the inflammatory response. Chromosome 12q contains two genes that could influence atopy and airway hyperresponsiveness, including nitric oxide synthase.

**STIMULI THAT INCITE ASTHMA** The stimuli that incite acute episodes of asthma can be grouped into seven major categories: allergenic, pharmacologic, environmental, occupational, infectious, exercise-related, and emotional.

**Allergens** Allergic asthma is dependent on an IgE response controlled by T and B lymphocytes and activated by the interaction of antigen with mast cell-bound IgE molecules. The airway epithelium and submucosa contain dendritic cells that capture and process antigen. After taking up an immunogen, these cells migrate to the local lymph nodes where they present the material to T cell receptors. In the appropriate genetic setting, the interaction of antigen with a naïve T cell T<sub>H</sub>0 in the presence of IL-4 leads to the differentiation of the cell to a T<sub>H</sub>2 subset. This process not only helps facilitate the inflammation of asthma but also causes B lymphocytes to switch their antibody production from IgG and IgM to IgE.

Once synthesized and released by B cells, IgE circulates in the blood until it attaches to high-affinity receptors on mast cells and low-affinity receptors on basophils. Most of the allergens that provoke asthma are airborne, and to induce a state of sensitivity they must be reasonably abundant for considerable periods of time. Once sensitization has occurred, however, the patient can exhibit exquisite responsiveness, so that minute amounts of the offending agent can produce significant exacerbations of the disease. Immune mechanisms appear to be causally related to the development of asthma in 25 to 35% of all cases and to be contributory in perhaps another third. Higher prev-



**FIGURE 236-3** Cytokine network in allergic asthma. IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; RANTES, regulated on activation, T cell expressed and secreted; TNF, tumor necrosis factor; SCS, stem cell factor. [From P. Barnes, in E Middleton et al (eds): *Allergy Principles and Practice*, 5th ed. St. Louis, Mosby, 1998, with permission.]

alences have been suggested, but it is difficult to know how to interpret the data because of confounding factors. Allergic asthma is frequently seasonal, and it is most often observed in children and young adults. A nonseasonal form may result from allergy to feathers, animal danders, dust mites, molds, and other environmental antigens that are present continuously. Exposure to antigen typically produces an immediate response in which airway obstruction develops in minutes and then resolves. In 30 to 50% of patients, a second wave of bronchoconstriction, the so-called late reaction, develops 6 to 10 h later. In a minority, only a late reaction occurs. It was formerly thought that the late reaction was essential to the development of the increase in airway reactivity that follows antigen exposure. This is now known not to be the case.

The mechanism by which an inhaled allergen provokes an acute episode of asthma depends in part on antigen-antibody interactions on the surface of pulmonary mast cells, with the subsequent generation and release of the mediators of immediate hypersensitivity. Current hypotheses hold that very small antigenic particles penetrate the lung's defenses and come in contact with mast cells that interdigitate with the epithelium at the luminal surface of the central airways. The subsequent elaboration of mediators and cytokines then produces the sequence outlined above.

**Pharmacologic Stimuli** The drugs most commonly associated with the induction of acute episodes of asthma are aspirin, coloring agents such as tartrazine,  $\beta$ -adrenergic antagonists, and sulfiting agents. It is important to recognize drug-induced bronchial narrowing because its presence is often associated with great morbidity. Furthermore, death sometimes has followed the ingestion of aspirin (or other nonsteroidal anti-inflammatory agents) or  $\beta$ -adrenergic antagonists. The typical aspirin-sensitive respiratory syndrome primarily affects adults, although the condition may occur in childhood. This problem usually begins with perennial vasomotor rhinitis that is followed by a hyperplastic rhinosinusitis with nasal polyps. Progressive asthma then appears. On exposure to even very small quantities of aspirin, affected individuals typically develop ocular and nasal congestion and acute, often severe episodes of airways obstruction.

The prevalence of aspirin sensitivity in patients with asthma varies from study to study, but many authorities feel that 10% is a reasonable figure. There is a great deal of cross-reactivity between aspirin and other nonsteroidal anti-inflammatory compounds that inhibit prostaglandin G/H synthase 1 (cyclooxygenase type 1). Indomethacin, fenoprofen, naproxen, zomepirac sodium, ibuprofen, mefenamic acid, and phenylbutazone are particularly important in this regard. However, acetaminophen, sodium salicylate, choline salicylate, salicylamide, and propoxyphene are well tolerated. The exact frequency of cross-reactivity to tartrazine and other dyes in aspirin-sensitive individuals with asthma is also controversial; again, 10% is the commonly accepted figure. This peculiar complication of aspirin-sensitive asthma is particularly insidious, however, in that tartrazine and other potentially troublesome dyes are widely present in the environment and may be unknowingly ingested by sensitive patients.

Patients with aspirin sensitivity can be desensitized by daily administration of the drug. After this form of therapy, cross-tolerance also develops to other nonsteroidal anti-inflammatory agents. The mechanism by which aspirin and other such drugs produce bronchospasm appears to be a chronic overexcretion of cysteinyl leukotrienes, which activate mast cells. The adverse reaction to aspirin can be inhibited with the use of leukotriene synthesis blockers or receptor antagonists.

$\beta$ -Adrenergic antagonists regularly obstruct the airways in individuals with asthma as well as in others with heightened airway reactivity and should be avoided by such individuals. Even the selective beta<sub>1</sub> agents have this propensity, particularly at higher doses. In fact, the local use of beta<sub>1</sub> blockers in the eye for the treatment of glaucoma has been associated with worsening asthma.

Sulfiting agents, such as potassium metabisulfite, potassium and sodium bisulfite, sodium sulfite, and sulfur dioxide, which are widely used in the food and pharmaceutical industries as sanitizing and preserving agents, can also produce acute airway obstruction in sensitive individuals. Exposure usually follows ingestion of food or beverages containing these compounds, e.g., salads, fresh fruit, potatoes, shellfish, and wine. Exacerbation of asthma has been reported after the use of sulfite-containing topical ophthalmic solutions, intravenous glucocorticoids, and some inhalational bronchodilator solutions. The incidence and mechanism of action of this phenomenon are unknown. When suspected, the diagnosis can be confirmed by either oral or inhalational provocations.

**Environment and Air Pollution** (See also Chap. 238) Environmental causes of asthma are usually related to climatic conditions that promote the concentration of atmospheric pollutants and antigens. These conditions tend to develop in heavily industrial or densely populated urban areas and are frequently associated with thermal inversions or other situations creating stagnant air masses. In these circumstances, although the general population can develop respiratory symptoms, patients with asthma and other respiratory diseases tend to be more severely affected. The air pollutants known to have this effect are ozone, nitrogen dioxide, and sulfur dioxide. All produce greater effects during periods of high ventilation. In some regions of North America, seasonal concentrations of airborne antigens such as pollen can rise high enough to result in epidemics of asthma admissions to hospitals and an increase in the death rate. These events may be ameliorated by treating patients prophylactically with anti-inflammatory drugs before the allergy season begins.

**Occupational Factors** (See also Chap. 238) Occupation-related asthma is a significant health problem, and acute and chronic airway obstruction have been reported to follow exposure to a large number of compounds used in many types of industrial processes. In general, the agents can be classified into high-molecular-weight compounds, which are believed to induce asthma through immunologic mechanisms, and low-molecular-weight agents, which serve as haptens or can release bronchoconstrictor substances. High-molecular-weight compounds of importance are *wood and vegetable dusts* (e.g., those of oak, grain, flour, castor bean, green coffee bean, mako, gum acacia, karaya, gum, and tragacanth), *pharmaceutical agents* (e.g., antibiotics, piperazine, and cimetidine), *biologic enzymes* (e.g., laundry detergents, pancreatic enzymes, and *Bacillus subtilis*), and *animal and insect dusts, serums, and secretions* (e.g., laboratory animals, chickens, crabs, prawns, oysters, flies, bees, and moths). Troublesome low-molecular-weight compounds are *metal salts* (e.g., platinum, chrome, vanadium, and nickel) and *industrial chemicals and plastics* (e.g., toluene diisocyanate, phthalic acid anhydride, trimellitic anhydride, persulfates, ethylene-diamine, *p*-phenylenediamine, western red cedar, azidrocyanamide, and various dyes). Formaldehyde and urea formaldehyde also fall into this group. It is important to recognize that exposure to sensitizing chemicals, particularly those used in paints, solvents, and plastics, can also occur during leisure or non-work-related activities.

If the occupational agent causes an immediate or dual immunologic reaction, the history is similar to that which occurs with exposure to other antigens. Often, however, patients will give a characteristic cyclic history. They are well when they arrive at work, and symptoms develop toward the end of the shift, progress after the work site is left, and then regress. Absence from work during weekends or vacations brings about remission. Frequently, there are similar symptoms in fellow employees.

**Infections** Respiratory infections are the most common of the stimuli that evoke acute exacerbations of asthma. Respiratory viruses and not bacteria or allergy to microorganisms are the major etiologic factors. In young children, the most important infectious agents are respiratory syncytial virus and parainfluenza virus. In older children and adults, rhinovirus and influenza virus predominate as pathogens. Simple colonization of the tracheobronchial tree is insufficient to evoke acute episodes of bronchospasm, and attacks of asthma occur only when

symptoms of an ongoing respiratory tract infection are, or have been, present. Viral infections can actively and chronically destabilize asthma, and they are perhaps the only stimuli that can produce constant symptoms for weeks. The mechanism by which viruses induce exacerbations of asthma may be related to the production of T cell-derived cytokines that potentiate the infiltration of inflammatory cells into already susceptible airways.

**Exercise** Exercise is a very common precipitant of acute episodes of asthma. This stimulus differs from other naturally occurring provocations, such as antigens, viral infections, and air pollutants, in that it does not evoke any long-term sequelae, nor does it increase airway reactivity. Typically the attacks follow exertion and do not occur during it. The critical variables that determine the severity of the postexertional airway obstruction are the levels of ventilation achieved and the temperature and humidity of the inspired air. The higher the ventilation and the lower the heat content of the air, the greater the response. For the same inspired air conditions, running produces a more severe attack of asthma than walking because of its greater ventilatory cost. Conversely, for a given task, the inhalation of cold air markedly enhances the response, while warm, humid air blunts or abolishes it. Consequently, activities such as ice hockey, cross-country skiing, and ice skating (high ventilations of cold air) are more provocative than is swimming in an indoor, heated pool (relatively low ventilation of humid air). The mechanism by which exercise produces obstruction may be related to a thermally produced hyperemia and capillary leakage in the airway wall.

**Emotional Stress** Psychological factors can worsen or ameliorate asthma. Changes in airway caliber seem to be mediated through modification of vagal efferent activity, but endorphins may also play a role. The extent to which psychological factors participate in the induction and/or continuation of any given acute exacerbation is not established but probably varies from patient to patient and in the same patient from episode to episode.

**PATHOLOGY** In a patient who has died of acute asthma, the most striking feature of the lungs at necropsy is their gross overdistention and failure to collapse when the pleural cavities are opened. When the lungs are cut, numerous gelatinous plugs of exudate are found in most of the bronchial branches down to the terminal bronchioles. Histologic examination shows hypertrophy of the bronchial smooth muscle, hyperplasia of mucosal and submucosal vessels, mucosal edema, denudation of the surface epithelium, pronounced thickening of the basement membrane, and eosinophilic infiltrates in the bronchial wall. There is an absence of any of the well-recognized forms of destructive emphysema.

**PATOPHYSIOLOGY** The pathophysiologic hallmark of asthma is a reduction in airway diameter brought about by contraction of smooth muscle, vascular congestion, edema of the bronchial wall, and thick, tenacious secretions. The net result is an increase in airway resistance, a decrease in forced expiratory volumes and flow rates, hyperinflation of the lungs and thorax, increased work of breathing, alterations in respiratory muscle function, changes in elastic recoil, abnormal distribution of both ventilation and pulmonary blood flow with mismatched ratios, and altered arterial blood gas concentrations. Thus, although asthma is considered to be primarily a disease of airways, virtually all aspects of pulmonary function are compromised during an acute attack. In addition, in very symptomatic patients there frequently is electrocardiographic evidence of right ventricular hypertrophy and pulmonary hypertension. When a patient presents for therapy, the 1-s forced expiratory volume (FEV<sub>1</sub>) or peak expiratory flow rate (PEFR) is typically <40% of predicted. In keeping with the alterations in mechanics, the associated air trapping is substantial. In acutely ill patients, residual volume frequently approaches 400% of normal, while functional residual capacity doubles.

Hypoxia is a universal finding during acute exacerbations, but frank ventilatory failure is relatively uncommon, being observed in 10 to 15% of patients presenting for therapy. Most individuals with asthma

have hypocapnia and a respiratory alkalosis. In acutely ill patients, the finding of a normal arterial carbon dioxide tension tends to be associated with quite severe levels of obstruction. Consequently, when found in a symptomatic individual, it should be viewed as representing impending respiratory failure, and the patient should be treated accordingly. Equally, the presence of metabolic acidosis in the setting of acute asthma signifies severe obstruction. Cyanosis is a very late sign. Trying to judge the state of an acutely ill patient's ventilatory status on clinical grounds alone can be extremely hazardous, and clinical indicators should not be relied on with any confidence. Therefore, in patients with suspected alveolar hypoventilation, arterial blood gas tensions must be measured.

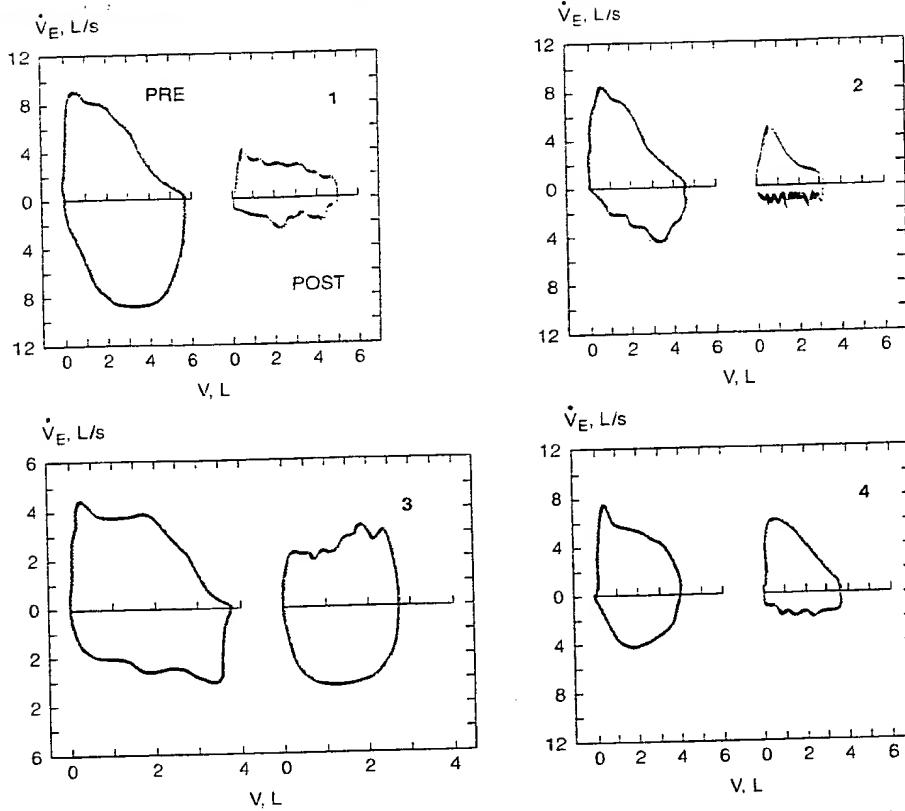
**CLINICAL FEATURES** The symptoms of asthma consist of a triad of dyspnea, cough, and wheezing, the last often being regarded as the *sine qua non*. In its most typical form, all three symptoms coexist. At the onset of an attack, patients experience a sense of constriction in the chest, often with a nonproductive cough. Respiration becomes audibly harsh; wheezing in both phases of respiration becomes prominent; expiration becomes prolonged; and patients frequently have tachypnea, tachycardia, and mild systolic hypertension. The lungs rapidly become overinflated, and the anteroposterior diameter of the thorax increases. If the attack is severe or prolonged, there may be a loss of adventitious breath sounds, and wheezing becomes very high pitched. Furthermore, the accessory muscles become visibly active, and a paradoxical pulse often develops. These two signs are extremely valuable in indicating the severity of the obstruction. In the presence of either, pulmonary function tends to be significantly more impaired than in their absence. It is important to note that the development of a paradoxical pulse depends on the generation of large negative intrathoracic pressures. Thus, if the patient's breathing is shallow, this sign and/or the use of accessory muscles could be absent even though obstruction is quite severe. The other signs and symptoms of asthma only imperfectly reflect the physiologic alterations that are present. Indeed, if the disappearance of subjective complaints or even of wheezing is used as the end point at which therapy for an acute attack is terminated, an enormous reservoir of residual disease will be missed.

The end of an episode is frequently marked by a cough that produces thick, stringy mucus, which often takes the form of casts of the distal airways (Curschmann's spirals) and, when examined microscopically, often shows eosinophils and Charcot-Leyden crystals. In extreme situations, wheezing may lessen markedly or even disappear, cough may become extremely ineffective, and the patient may begin a gasping type of respiratory pattern. These findings imply extensive mucus plugging and impending suffocation. Ventilatory assistance by mechanical means may be required. Atelectasis due to inspissated secretions occasionally occurs with asthmatic attacks. Spontaneous pneumothorax and/or pneumomediastinum occur but are rare.

Less typically, a patient with asthma may complain of intermittent episodes of nonproductive cough or exertional dyspnea. Unlike other individuals with asthma, when these patients are examined during symptomatic periods, they tend to have normal breath sounds but may wheeze after repeated forced exhalations and/or may show ventilatory impairments when tested in the laboratory. In the absence of both these signs, a bronchoprovocation test may be required to make the diagnosis.

**DIFFERENTIAL DIAGNOSIS** The differentiation of asthma from other diseases associated with dyspnea and wheezing is usually not difficult, particularly if the patient is seen during an acute episode. The physical findings and symptoms listed above and the history of periodic attacks are quite characteristic. A personal or family history of allergic diseases such as eczema, rhinitis, or urticaria is valuable contributory evidence. An extremely common feature of asthma is nocturnal awakening with dyspnea and/or wheezing. In fact, this phenomenon is so prevalent that its absence raises doubt about the diagnosis.

*Upper airway obstruction by tumor or laryngeal edema can occa-*



**FIGURE 236-4** Representative examples of glottic dysfunction in four patients. The left-hand panels show normal flow-volume curves (red). The right-hand panels (green) represent the development of glottic dysfunction after exercise challenges (green). Note the variable waveforms that can exist. When the patients' attacks ended, the post provocation flow-volume curves returned to normal.  $\dot{V}_E$ , ventilation; L/s, liters/second; V, lung volume in liters.

sionally be confused with asthma. Typically, a patient with such a condition will present with stridor, and the harsh respiratory sounds can be localized to the area of the trachea. Representative flow-volume curves are shown in Fig. 236-4. Diffuse wheezing throughout both lung fields is usually absent. However, differentiation can sometimes be difficult, and indirect laryngoscopy or bronchoscopy may be required. Asthma-like symptoms have been described in patients with glottic dysfunction. These individuals narrow their glottis during inspiration and expiration, producing episodic attacks of severe airway obstruction. Occasionally, carbon dioxide retention develops. However, unlike in asthma, the arterial oxygen tension is well preserved, and the alveolar-arterial gradient for oxygen narrows during the episode, instead of widening as with lower airway obstruction. To establish the diagnosis of glottic dysfunction, the glottis should be examined when the patient is symptomatic. Normal findings at such a time exclude the diagnosis; normal findings during asymptomatic periods do not.

Persistent wheezing localized to one area of the chest in association with paroxysms of coughing indicates endobronchial disease such as foreign-body aspiration, a neoplasm, or bronchial stenosis.

The signs and symptoms of acute left-ventricular failure occasionally mimic asthma, but the findings of moist basilar rales, gallop rhythms, blood-tinged sputum, and other signs of heart failure (Chap. 216) allow the appropriate diagnosis to be reached.

Recurrent episodes of bronchospasm can occur with carcinoid tumors (Chap. 329), recurrent pulmonary emboli (Chap. 244), and chronic bronchitis (Chap. 242). In chronic bronchitis there are no true symptom-free periods, and one can usually obtain a history of chronic cough and sputum production as a background on which acute attacks of wheezing are superimposed. Recurrent emboli can be very difficult to separate from asthma. Frequently, patients with this condition present with episodes of breathlessness, particularly on exertion, and

they sometimes wheeze. Lung scans may not be diagnostic because of the ventilation-perfusion abnormalities characteristic of asthma, and pulmonary angiography may be necessary to establish the correct diagnosis.

**Eosinophilic pneumonias** (Chap. 237) are often associated with asthmatic symptoms, as are various chemical pneumonias and exposures to insecticides and cholinergic drugs. Bronchospasm is occasionally a manifestation of *systemic vasculitis* with pulmonary involvement.

**DIAGNOSIS** The diagnosis of asthma is established by demonstrating reversible airway obstruction. **Reversibility** is traditionally defined as a  $\geq 15\%$  increase in  $FEV_1$  after two puffs of a  $\beta$ -adrenergic agonist. When the spirometry results are normal at presentation, the diagnosis can be made by showing heightened airway responsiveness to challenges with histamine, methacholine, or isocapnic hyperventilation of cold air. Once the diagnosis is confirmed, the course of the illness and the effectiveness of therapy can be followed by measuring PEFRs at home and/or the  $FEV_1$  in the office or laboratory. Positive wheal-and-flare reactions to skin tests can be demonstrated to various allergens, but such findings do not necessarily correlate with the intrapulmonary events. Sputum and blood eosinophilia and measurement of serum IgE levels are also helpful but are not specific for asthma. Chest roentgenograms showing hyperinflation are also nondiagnostic.

## Rx TREATMENT

Elimination of the causative agent(s) from the environment of an allergic individual with asthma is the most successful means available for treating this condition (for details on avoidance, see Chap. 298). Desensitization or immunotherapy with extracts of the suspected allergens has enjoyed widespread favor, but controlled studies are limited and have not proved to be highly effective.

**DRUG TREATMENT** The available agents for treating asthma can be divided into two general categories: drugs that inhibit smooth-muscle contraction, i.e., the so-called "quick relief medications" ( $\beta$ -adrenergic agonists, methylxanthines, and anticholinergics) and agents that prevent and/or reverse inflammation, i.e., the "long-term control medications" (glucocorticoids, long-acting  $\beta_2$ -agonists, combined medications, mast cell-stabilizing agents, leukotriene modifiers, and methylxanthines) (Table 236-1).

**Quick Relief Medications ■ ADRENERGIC STIMULANTS** The drugs in this category consist of the catecholamines, resorcinols, and saligenins. These agents produce airway dilation through stimulation of  $\beta$ -adrenergic receptors and activation of G proteins with the resultant formation of cyclic adenosine monophosphate (AMP). They also decrease release of mediators and improve mucociliary transport. The catecholamines (epinephrine, isoproterenol, and isoproterenol) are short-acting (30 to 90 min) and are effective only when administered by inhalational or parenteral routes. Their use has been superseded by the longer acting selective  $\beta_2$ -agonists terbutaline, fenoterol (a resorcinol), and albuterol (a saligenin). The resorcinols and saligenins are highly selective for the respiratory tract and are virtually devoid of significant cardiac effects except at high doses.

Their major side effect is tremor. They are active by all routes of administration and are relatively long-lasting (4 to 6 h). Inhalation is the preferred route because it allows maximal bronchodilation with fewer side effects. In treating episodes of severe asthma, intravenous administration offers no advantages over the inhaled route.